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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number
WO 2006/138449 A2

(51) International Patent Classification:
G01N 33/574 (2006.01)

(21) International Application Number:
PCT/US2006/023288

(22) International Filing Date: 15 June 2006 (15.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/691,029 16 June 2005 (16.06.2005) US

(71) Applicant *(for all designated States except US)*: **THE WISTAR INSTITUTE** [US/US]; 3601 Spruce Street, Philadelphia, PA 19104-4268 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HERLYN, Dorothee** [US/US]; 1223 Knox Road, Wynnewood, PA 19096 (US). **SOMASUNDARAM, Rajasekharan** [US/US]; 421 Gateswood Drive, West Chester, PA 19380 (US). **SWOBODA, Rolf, K.** [DE/US]; 109 Crestview Road, Upper Darby, PA 19082 (US).

(74) Agent: **LICATA, Jane, Massey**; LICATA & TYRRELL P.C., 66 E. Main Street, Marlton, NJ 08053 (US).

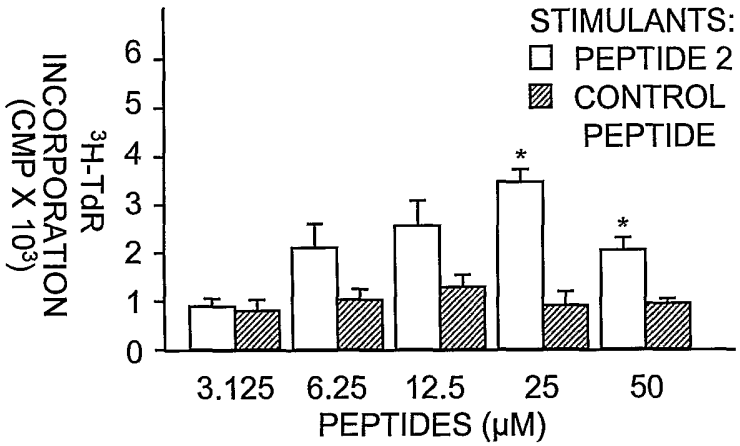
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** METHOD FOR IDENTIFYING A MHC CLASS II-DEPENDENT TUMOR-ASSOCIATED T HELPER CELL ANTIGEN



(57) **Abstract:** The present invention is a method for identifying MHC class II-dependent disease-associated antigens. The instant method involves expressing a library of disease-derived proteins in lytic bacteriophage for subsequent presentation by antigen presenting cells to T helper cells. Disease- associated antigens are provided as are the use of such antigens in vaccines for inducing an immune response and preventing or treating disease. Moreover, the present invention provides antibodies, which specifically bind to MHC class II -dependent disease-associated antigens or epitope peptides thereof, and their diagnostic and therapeutic use.

WO 2006/138449 A2

METHOD FOR IDENTIFYING A MHC CLASS II-DEPENDENT TUMOR-ASSOCIATED T HELPER CELL ANTIGEN

Introduction

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/691,029, filed June 16, 2005, the content of which is incorporated herein by reference in its entirety.

This invention was made in the course of research sponsored by the National Institutes of Health (Grant Nos. CA93372-02, CA60975, CA88193, CA25874, CA10815). The U.S. government may have certain rights in this invention.

Background of the Invention

$CD4^+$ T helper (Th) lymphocytes play a central role in the development of protective immunity against tumors and infectious agents. Adoptively transferred $CD4^+$ T helper cells, in the absence of $CD8^+$ cytolytic T lymphocytes (CTL), inhibit tumor growth in mice (Baskar, et al. (1995) *J. Exp. Med.* 181:619-29; Dranoff, et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:3539-43; Hung, et al. (1998) *J. Exp. Med.* 188:2357-68; Levitsky, et al. (1994) *J. Exp. Med.* 179:1215-24). Furthermore, the immunotherapeutic potential of MHC class II-associated, tumor-derived peptides has been demonstrated in experimental animals (Hunt, et al. (1992) *Science* 256:1817-20; Rudensky, et al. (1991) *Nature* 353:622-7). In melanoma patients, spontaneous tumor regression is associated with $CD4^+$ lymphocyte infiltrates (Clemente, et al. (1996) *Cancer* 77:1303-10; Fischer, et al. (1999) *Cancer Immunol. Immunother.* 48:363-70). In allogeneic bone marrow transplant patients, the *in vivo* persistence of adoptively transferred cytomegalovirus-specific $CD8^+$ T cells is

dependent on an endogenous $CD4^+$ T-cell response (Walter, et al. (1995) *N. Engl. J. Med.* 333:1038-44).

Knowledge of defined human leukocyte antigen (HLA) class II-dependent T helper cell antigens in infectious disease and tumor systems is lacking. Such antigens have great potential for inducing protective immune responses. A few human $CD4^+$ T helper cell lines and clones directed against various tumors have been described (Radrizzani, et al. (1991) *Int. J. Cancer* 49:823-30; Takahashi, et al. (1995) *J. Immunol.* 154:772-9; Topalian, et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:9461-5; Topalian, et al. (1994) *Int. J. Cancer* 58:69-79; Wang (2001) *Trends Immunol.* 22:269-76). T helper antigens are usually recognized by major histocompatibility complex (MHC) class II-restricted $CD4^+$ T helper cells after processing by antigen-presenting cells (APC) through the exogenous pathway (Schwartz (1985) *Annu. Rev. Immunol.* 3:237-61). Although expression cloning of MHC class II antigens in *E. coli* has been successful in bacterial and parasitic antigen systems (Sanderson, et al. (1995) *J. Exp. Med.* 182:1751-7; Mougneau, et al. (1995) *Science* 268:563-6), this approach has limitations in its application to the human system because of the great complexity of the human genome (Darnell & Baltimore (1986) In: *Molecular and Cellular Biology*, eds. Lodish, et al., Scientific American Books, New York, pp. 151-188).

The conventional molecular cloning approach of HLA class II-dependent human melanoma and colon carcinoma antigens is based on fusing cDNA tumor libraries to MHC invariant chain (Ii) fragments with the aim of targeting the fusion proteins to the endosomal and lysosomal compartments (Wang (2001) *supra*) which is necessary for the proteins to be presented in association with MHC class II molecules. Fused libraries are transfected into 293 cells genetically engineered to express DRα, DRβ, DMA, DMB, and Ii and screened for reactivity with

$CD4^+$ T cells. Using this or slightly modified approaches, six mutated, individual-specific antigens, namely mutated CDC27 (Wang, et al. (1999) *Science* 284:1351-4), fusion gene LDLR-FUT (Wang, et al. (1999) *J. Exp. Med.* 189:1659-68), mutated fibronectin (Wang, et al. (2002) *J. Exp. Med.* 195:1397-406), mutated NeoPAP (Topalian, et al. (2002) *Cancer Res.* 62:5505-9), mutated PTPRK (Novellino, et al. (2003) *J. Immunol.* 170:6363-70), and mutated ARTC1 (Wang, et al. (2005) *J. Immunol.* 174:2661-70) have been identified in melanoma and colorectal carcinoma patients, as have two shared antigens (among patients with the same tumor type), namely COA-1 and EphA3 (Maccalli, et al. (2003) *Cancer Res.* 63:6735-43; Chiari, et al. (2000) *Cancer Res.* 60:4855-63). Thus, only two class II-restricted antigens with immunotherapeutic potential for a larger population of patients emerged from these studies.

Needed is a robust method for identifying tumor-associated T helper cell antigens without prior knowledge of the MHC class II restriction elements for use in vaccines for preventing or treating cancer. The present invention meets this need in the art.

Summary of the Invention

The present invention is a method for identifying a MHC class II-dependent disease-associated T helper cell antigen. The method involves the steps of expressing a library of disease-derived proteins in lytic bacteriophage; presenting antigens of the library of disease-derived proteins on the surface of MHC class II-positive antigen presenting cells (APC); contacting the APC with T helper cells and determining T helper cell recognition, wherein the recognition by a T helper cells is indicative of said APC presenting a MHC class II-dependent disease-associated T helper cell antigen.

An MHC class II-dependent disease-associated T helper cell antigen and vaccine containing the same are provided as are methods for inducing an immune response to a MHC class II-dependent disease-associated T helper cell antigen and preventing or treating cancer or infectious disease.

Certain embodiments also embrace antibodies which specifically bind to a MHC class II-dependent disease-associated T helper cell antigen or epitope peptide thereof and their use in methods for preventing or treating cancer or infectious disease.

Brief Description of the Drawings

Figure 1 depicts the Ii-cDNA fusion approach (Figure 1A) (Wang, et al. (1999) *supra*) and instant bacteriophage-cDNA fusion approach (Figure 1B) for identifying tumor-associated T helper cell antigens.

Figure 2 shows that the recognition of RPL8 peptide #2 by Th35-1A cells is HLA DR7- and peptide concentration-dependent. Figure 2A, Th35-1A cells were stimulated with peptide (between 3.1 and 50 μM)-pulsed autologous $DR7^+$ monocytes in the absence of antibody or presence of either control mouse immunoglobulin (Ig) or anti-HLA class II antibody (both at 10 μg/mL). Th35-1A cells were stimulated with peptide (various concentrations)-pulsed autologous monocytes (Figure 2B), $DR7^+$ allogeneic monocytes (Figure 2C), or $DR7^-$ allogeneic monocytes (Figure 2D). Proliferation of Th35-1A cells was measured by $[^3H]$-thymidine (TdR) incorporation assay. Values with identical symbols (*,#) differ significantly ($p<0.01$) from each other (Figure 2A). * denotes experimental values that differ significantly ($p<0.01$) from the corresponding control values (Figures 2B and 2C).

Figure 3 shows proliferative lymphocyte responses to RPL8 peptide #2 stimulation in PBMC of $DR7^+$ melanoma patients. Figures 3A-3C, PBMC from three $DR7^+$ melanoma patients were stimulated twice with autologous monocytes pulsed with peptide #2 or control peptide, and proliferation ($[^3H]$-TdR incorporation) in PBMC was determined. PBMC from two $DR7^-$ melanoma patients (Figure 3D and 3E) and four healthy donors (Figure 3F, only one shown) did not respond after one peptide stimulation. Due to lack of surviving cells after the first round of peptide stimulation, PBMC of $DR7^-$ patients or healthy donors could not be stimulated a second time.

Detailed Description of the Invention

A novel method for identifying disease-associated T helper cell antigens has now been developed. The inventive method involves expressing a library of disease-derived proteins in lytic bacteriophage; presenting the library of disease-derived proteins on the surface of MHC class II-positive antigen presenting cells (APC); contacting the APC with T helper cells and determining T helper cell stimulation, wherein the stimulation of a T helper cell by an APC is indicative of said APC presenting a MHC class II-dependent disease-associated T helper cell antigen (see Figure 1A). In contrast to conventional methods (Figure 1B), the instant method provides natural processing of phage-expressed antigen by antigen-presenting cells (APCs) and is not independent on prior knowledge of the MHC restriction molecule used by T helper cells for antigen recognition. Accordingly, relevant disease epitopes are identified which find application in vaccines for the prevention or treatment of diseases such as cancer or infectious disease.

By way of illustration, the instant method was applied to the identification of a melanoma-asociated antigen. Th35-1A cells recognize an antigen expressed by melanoma and glioma cells (Somasundaram, et al. (2003) *Int. J. Cancer* 104:362-8). A cDNA library from WM35 melanoma cells was expressed by T7 phage, APC (EBV-B35 cells) presented phage-library protein to Th35-1A lymphocytes, and the relevant T helper antigen was identified by its capacity to induce proliferation and interferon-γ release in Th35-1A cells. A stimulatory phage clone was identified. The clone had an insert of 185 bp and encoded the C-terminal part of ribosomal protein (RP) L8 (Hanes, et al. (1993) *Biochem. Biophys. Res. Commun.* 197:1223-8; GENBANK Accession No. GI:15082585; SEQ ID NO:1). The cDNA encoded an open reading frame of 58 amino acids.

To confirm that RPL8 was recognized by Th35-1A, the peptide epitope recognized by Th35-1A was determined. This epitope was predicted to associate with HLA DR7, as Th35-1A recognizes antigen in association with DR7 (Somasundaram, et al. (2003) *supra*). The deduced amino acid sequence of the cloned cDNA contains two potential DR7 (DRB1*070101) binding sites (Rammensee, et al. (1999) *Immunogenetics* 50:213-9). Two overlapping peptides (#1, Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr; SEQ ID NO:2 and #2, Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys-Glu-Asn; SEQ ID NO:3) with high HLA DR7 binding scores (>20) were synthesized and used for stimulation of Th35-1A cells. Peptide #2 (SEQ ID NO:3) was recognized by Th35-1A after presentation by autologous monocytes, and peptide recognition was HLA class II-dependent (Figure 2A). Th35-1A proliferation was peptide concentration-dependent (Figure 2B). Allogeneic $DR7^+$ monocytes presented peptide #2 to Th35-1A cells (Figure 2C), whereas $DR7^-$ monocytes did not (Figure 2D).

The data disclosed herein indicate that Th35-1A recognizes RPL8. RPL8 protein (28 kDa) is a component of the 60S subunit of ribosomes and is involved in protein synthesis. It is expressed by all normal cells and ovarian carcinomas (Luo, et al. (2002) *Br. J. Cancer* 87:339-43). RPL8 RNA is overexpressed in metastatic versus primary carcinomas (Futschik, et al. (2002) *Genome Lett.* 1:26-34). In light of the ubiquitous expression of RPL8, it was unexpected that some, but not all, tumor cell lysates derived from different patients stimulated proliferation of Th35-1A, although the non-stimulatory tumor cells expressed RPL8 RNA (Table 1) (Somasundaram, et al. (2003) *supra*).

TABLE 1

Cell Name	Cell Type	Relative RPL8 RNA Abundance[1]	Reactivity of Cell Lysate with Th35-1A[2]
FOM 124-1	Melanocyte	0.45	n.d.[3]
FOM 125-1	Melanocyte	0.54	n.d.
WM35	Melanoma	1.00	positive
1205LU	Melanoma	1.50	positive
WM115	Melanoma	0.84	n.d.
WM3450	Melanoma	0.93	n.d.
WM3526	Melanoma	1.65	n.d.
WM3623	Melanoma	1.54	n.d.
WM793	Melanoma	0.92	positive
WC020	Colon Carcinoma	1.44	n.d.
U87MG	Glioma	5.00	positive
U373MG	Glioma	4.50	positive
K562	Erythroleukemia	0.36	negative
Daudi	Lymphoma	1.10	negative
293	Human Primary Embryonal Kidney	1.87	n.d.

[1] The value of WM35 RNA was set at 1 and the abundance of RNA in the other cells was calculated relative to this value.
[2] Somasundaram, et al. (2003) *supra*.
[3] n.d., not determined.

The nucleotide sequence of full-length RPL8 subsequently cloned from WM35 melanoma cells was 100% identical with the published RPL8 sequence (GENBANK GI:15082585; SEQ ID NO:4). While an antibody to RPL8 was not available to determine RPL8

protein levels in tumors of various tissue origins, RPL8 protein is expressed by melanoma, glioma (as evidenced by recognition of these tumor cells by Th35-1A29) and ovarian carcinoma (Luo, et al. (2002) *supra*).

To demonstrate that RPL8 peptide #2 finds application in a vaccine for melanoma patients in addition to patient 35, peripheral blood monocytes from three $DR7^+$ melanoma patients were pulsed with the peptide, and proliferation of autologous PBMC following peptide stimulation was determined in $[^3H]$-thymidine incorporation assays. Lymphocytes from two $DR7^-$ melanoma patients and four healthy donors served as controls. Lymphocytes from two of the three $DR7^+$ melanoma patients (Figures 3A-3C) significantly and specifically proliferated to peptide stimulation, whereas neither of the two $DR7^-$ melanoma patients (Figures 3D and 3E) or four healthy donors (only one donor shown in Figure 3F) showed lymphoproliferative responses. The results obtained in proliferation assays (Figure 3) were confirmed in interferon-γ release assays. Thus, the proliferating lymphocytes from the two $DR7^+$ patients shown in Figure 3A and Figure 3B produced maximally 124.3 ± 1.67 pg and 224.3 ± 4.3 pg per mL of IFN-γ, respectively, whereas the non-proliferating lymphocytes from the two $DR7^-$ patients (Figures 3D and 3E) and healthy donor (Figure 3F) produced < 12 pg/mL of IFN-γ.

To demonstrate that RPL8 has potential as a vaccine for patients expressing HLA other than DR7, the Rammensee epitope prediction model was used to search for additional putative HLA class II- and class I-binding epitopes on full-length RPL8. Full-length RPL8 contained 27 additional DR7 binding epitopes, and multiple epitopes binding to 3 non-DR7 HLA class II and 7 HLA class I (Tables 2 and 3). Thus, many RPL8 peptides, in addition to peptide #2 and full-length RPL8, are

useful in vaccines for cancer patients whose tumors express RPL8, *e.g.*, melanomas, gliomas, and ovarian carcinomas.

TABLE 2

HLA Type[1]	Number of RPL8 Epitopes with a Binding Score ≥15	HLA Representation (% of US Population)[2]		
		African American	Caucasian	Asian
Class I				
A0101	6	5.56	15.09	1.53
A0201	35	12.30	27.17	9.47
A03	55	9.92	12.64	0.97
A2402	4	2.78	6.60	18.94
B0702	13	8.17	11.13	2.51
B4402	11	1.99	11.70	0.70
B5101	32	1.20	5.66	6.69
Class II				
DRB1*0101	89	6.82	10.22	3.46
DRB1*0401	34	5.70	16.75	15.46
DRB1*0701	28	10.13	13.28	6.92
DRB1*1101	39	10.61	9.31	4.73

[1] Only HLA types expressed by at least 5% of one of the three populations are shown.

[2] Cao, et al. (2001) *Human. Immunol.* 62:1009-1030; Mori, et al. (1997) *Transplantation* 64:1017-1027.

Table 3

RPL8 Epitope	Score	SEQ ID NO:
*HLA-A*01 nonamers*		
Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr	17	5
Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr	17	6
Gly-Ile-His-Thr-Gly-Gln-Phe-Val-Tyr	17	7
Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr	16	8
Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr	16	9
Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr	15	10
*HLA-A*0201 nonamers*		
Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val	24	11
Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val	24	12
Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile	22	13
Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val	21	14
Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val	20	15
Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val	20	16
Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val	20	17
Arg-Ile-Asp-Lys-Pro-Ile-Leu-Lys-Ala	20	18
Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu	20	19
Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly	19	20
Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val	19	21
Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu	19	22
Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val	18	23

Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile-Val	18	24
Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val	18	25
Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val	18	26
Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala	17	27
Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile	17	28
Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu	16	29
Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu	16	30
Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	16	31
Arg-Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val	16	32
Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala	15	33
Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val	15	34
Ala-Gly-Ser-Val-Phe-Arg-Ala-His-Val	15	35
Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu	15	36
Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr	15	37
Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu	15	38
Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro	15	39
Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu	15	40
Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly	15	41
Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile	15	42
Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His	15	43
Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile	15	44
Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly	15	45
*HLA-A*03 nonamers*		
Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys	29	46
Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His	25	47
Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr	24	48
Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro	24	49
Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg	24	50
Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln	24	51
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys	23	52
Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys	23	53
Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys	23	54
Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly	22	55
Ser-Val-Phe-Arg-Ala-His-Val-Lys-His	22	56
Arg-Leu-Arg-Ala-Val-Asp-Phe-Ala-Glu	21	57
Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro	21	58
Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys	21	59
Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe	20	60
Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys	20	61
Gly-Ile-His-Thr-Gly-Gln-Phe-Val-Tyr	20	62
Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr	20	63
Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys	20	64
Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His	20	65
Arg-Arg-Asp-Ala-Pro-Ala-Gly-Arg-Lys	20	66
Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly	20	67
Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe	19	68
Gly-Ser-Val-Phe-Arg-Ala-His-Val-Lys	19	69
Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg	19	70
Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro	19	71
Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala	19	72
Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly	19	73
Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg	19	74
Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe	18	75
Thr-Ile-Val-Cys-Cys-Leu-Glu-Glu-Lys	18	76
Cys-Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg	18	77
Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile	18	78
Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp	18	79
Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys	18	80
Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys	18	81

Thr-Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly	18	82
Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln	17	83
Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys	16	84
Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe-Arg	16	85
Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys	16	86
Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg	16	87
Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly-Lys	16	88
Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly	16	89
Gly-Arg-Ile-Asp-Lys-Pro-Ile-Leu-Lys	16	90
Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile	16	91
Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg	16	92
His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala	15	93
Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg	15	94
Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val	15	95
Pro-Glu-Thr-Lys-Lys-Thr-Arg-Val-Lys	15	96
Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val	15	97
Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly	15	98
Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys	15	99
Arg-Ile-Asp-Lys-Pro-Ile-Leu-Lys-Ala	15	100
*HLA-A*2402 nonamers*		
Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu	23	101
Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile	20	102
Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe	20	103
Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp	16	104
*HLA-B*0702 nonamers*		
Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu	27	105
Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met	22	106
Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile	21	107
Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala	20	108
Lys-Pro-Gly-Asp-Arg-Gly-Lys-Leu-Ala	19	109
Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala	18	110
Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg	17	111
Asn-Pro-Glu-Thr-Lys-Lys-Thr-Arg-Val	17	112
Lys-Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala	17	113
Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr	16	114
Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu	15	115
His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu	15	116
Glu-Thr-Lys-Lys-Thr-Arg-Val-Lys-Leu	15	117
*HLA-B*4402 nonamers*		
Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe	25	118
Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys-Leu	23	119
Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu	18	120
Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe	17	121
Ala-Met-Asn-Pro-Val-Glu-His-Pro-Phe	17	122
Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile	16	123
Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly-Lys	16	124
Glu-Lys-Pro-Gly-Asp-Arg-Gly-Lys-Leu	16	125
Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu	16	126
Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly	15	127
Glu-Thr-Lys-Lys-Thr-Arg-Val-Lys-Leu	15	128
*HLA-B*5101 nonamers*		
Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile	28	129
Asn-Pro-Glu-Thr-Lys-Lys-Thr-Arg-Val	23	130
Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile	23	131
Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val	21	132
Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val	21	133
Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr	20	134
Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly	20	135

Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val	19	136
Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val	19	137
Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile	19	138
Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile	19	139
Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu	19	140
Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile	19	141
Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu	18	142
Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val	18	143
Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg	17	144
Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly	17	145
Gly-Gly-Gly-Arg-Ile-Asp-Lys-Pro-Ile	17	146
Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile	17	147
Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile	16	148
Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro	16	149
Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile	16	150
Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	16	151
Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys	16	152
Ala-Gly-Ser-Val-Phe-Arg-Ala-His-Val	16	153
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys	15	154
Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala	15	155
Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe	15	156
Glu-Gly-Ile-His-Thr-Gly-Gln-Phe-Val	15	157
Met-Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys	15	158
Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala	15	159
Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile	15	160
*HLA-DRB1*0101 15 - mers*		
Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val	32	161
Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys	30	162
Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala	27	163
Arg-Ile-Asp-Lys-Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys	27	164
Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe	25	165
Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly	25	166
Asn-Arg-Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp	25	167
Arg-Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe-Ala-Glu-Arg	24	168
Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg	24	169
Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile	24	170
Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly	24	171
Arg-Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys	24	172
Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro	24	173
Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu	24	174
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro	23	175
Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala	22	176
Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu	22	177
Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys	22	178
Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr	22	179
Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp	21	180
Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu	21	181
Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile	21	182
Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro	21	183
Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe-Arg-Ala-His	20	184
Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe-Val-Tyr-Cys	20	185
Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met	20	186
Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys-Leu	20	187
Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly	20	188
Met-Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val	19	189
Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly	19	190
Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe	19	191
Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe-Val-Tyr-Cys-Gly	19	192
Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr	19	193

Lys-Pro-Gly-Asp-Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr	19	194
Lys-Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser	19	195
Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys-Pro-Ile	19	196
Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg	19	197
Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr	19	198
Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys	19	199
Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe-Arg	18	200
Ala-Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile-Val	18	201
His-Thr-Gly-Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn	18	202
Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn	18	203
Glu-Gly-Thr-Ile-Val-Cys-Cys-Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg	18	204
Gly-Thr-Ile-Val-Cys-Cys-Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly	18	205
Thr-Lys-Lys-Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val	18	206
Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys-Pro	18	207
Met-Asn-Pro-Val-Glu-His-Pro-Phe-Gly-Gly-Gly-Asn-His-Gln-His	18	208
Glu-His-Pro-Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro	18	209
Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly	18	210
Thr-Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile	18	211
Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu	18	212
Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe-Arg-Ala	17	213
Arg-Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala	17	214
Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val	17	215
Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys	17	216
Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val	17	217
Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp	17	218
Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly	17	219
Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly	17	220
Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser	17	221
Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn	17	222
Lys-Lys-Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile	17	223
Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser	17	224
Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala	17	225
Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val	17	226
Lys-Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala	17	227
Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His	17	228
Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro-Phe-Gly-Gly	17	229
Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg	17	230
Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp	17	231
Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg	17	232
Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe	16	233
Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr	16	234
Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val	16	235
Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro	16	236
Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala-Ala	16	237
Gly-Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly	16	238
Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val	16	239
Val-Cys-Cys-Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly-Lys-Leu-Ala	16	240
Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	16	241
Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro-Phe-Gly-Gly-Gly-Asn	16	242
Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile	16	243
His-Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala-Pro	16	244
Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg	16	245
Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys-Glu-Asn	16	246
Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala	15	247
Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr	15	248
Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val	15	248
*HLA-DRB1*0401 (DR4Dw4) 15 - mers*		
Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	26	249
Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu	22	250

Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe	22	251
Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys	22	252
Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val	22	253
Glu-His-Pro-Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro	22	254
Met-Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val	20	255
Leu-Arg-Ala-Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly	20	256
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro	20	257
Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala	20	258
Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala	20	259
Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr	20	260
Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu	20	261
Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile	20	262
Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile	20	263
Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val	20	264
Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys-Pro-Ile-Leu	20	265
Asp-Lys-Pro-Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys	20	266
Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro	20	267
Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro-Phe-Gly-Gly-Gly-Asn	20	268
Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu	20	269
Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly	20	270
Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe-Arg-Ala-His-Val-Lys-His-Arg	18	271
Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe	18	272
Arg-Ala-Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile	18	273
Lys-Lys-Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile	18	274
Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val	18	275
Ile-Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg	18	276
Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala	17	277
Gly-Ser-Val-Phe-Arg-Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala	16	278
Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp	16	279
Thr-Gly-Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile	16	280
Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro	16	281
Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr	15	282
*HLA-DRB1*0701 15 - mers*		
Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val	28	283
Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu	24	284
Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr	24	285
Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys-Glu-Asn	24	286
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro	22	287
Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys	22	288
Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser	22	289
Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	22	290
Leu-Arg-Ala-Val-Asp-Phe-Ala-Glu-Arg-His-Gly-Tyr-Ile-Lys-Gly	20	291
Arg-Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln	20	292
Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe-Val-Tyr-Cys	20	293
Arg-His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp	18	294
Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala	18	295
Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile	18	296
Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys	18	297
Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val	18	298
Glu-His-Pro-Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro	18	299
Thr-Glu-Leu-Phe-Ile-Ala-Ala-Glu-Gly-Ile-His-Thr-Gly-Gln-Phe	16	300
Gly-Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile-Gly	16	301
Lys-Ala-Gln-Leu-Asn-Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met	16	302
Ile-Gly-Asn-Val-Leu-Pro-Val-Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile	16	303
Gly-Thr-Met-Pro-Glu-Gly-Thr-Ile-Val-Cys-Cys-Leu-Glu-Glu-Lys	16	304
Ile-Ser-His-Asn-Pro-Glu-Thr-Lys-Lys-Thr-Arg-Val-Lys-Leu-Pro	16	305
Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala	16	306
Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg	16	307
Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro	16	308

His-Gln-His-Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala-Pro	16	309
Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys	16	310
*HLA-DRB1*1101 15 - mers*		
Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala	26	311
Gly-Val-Ala-Met-Asn-Pro-Val-Glu-His-Pro-Phe-Gly-Gly-Gly-Asn	26	312
His-Gly-Tyr-Ile-Lys-Gly-Ile-Val-Lys-Asp-Ile-Ile-His-Asp-Pro	23	313
Gly-Ser-Val-Phe-Arg-Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala	22	314
Ser-Val-Phe-Arg-Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg	22	315
Ser-Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys	22	316
Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe	21	317
Met-Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val	20	318
Gly-Arg-Val-Ile-Arg-Gly-Gln-Arg-Lys-Gly-Ala-Gly-Ser-Val-Phe	20	319
Lys-Asp-Ile-Ile-His-Asp-Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys	20	320
Pro-Gly-Asp-Arg-Gly-Lys-Leu-Ala-Arg-Ala-Ser-Gly-Asn-Tyr-Ala	20	321
Asn-Arg-Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp	20	322
Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly-Arg	20	323
Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu	19	324
Arg-Asp-Pro-Tyr-Arg-Phe-Lys-Lys-Arg-Thr-Glu-Leu-Phe-Ile-Ala	18	325
Thr-Gly-Gln-Phe-Val-Tyr-Cys-Gly-Lys-Lys-Ala-Gln-Leu-Asn-Ile	18	326
Gly-Thr-Ile-Val-Cys-Cys-Leu-Glu-Glu-Lys-Pro-Gly-Asp-Arg-Gly	18	327
Glu-His-Pro-Phe-Gly-Gly-Gly-Asn-His-Gln-His-Ile-Gly-Lys-Pro	18	328
Gly-Asn-Tyr-Ala-Thr-Val-Ile-Ser-His-Asn-Pro-Glu-Thr-Lys-Lys	17	329
Lys-Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro	17	330
Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu-Arg-Ala-Val-Asp-Phe	16	331
Pro-Glu-Thr-Lys-Lys-Thr-Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys	16	332
Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg	16	333
Lys-Ala-Lys-Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met	16	334
Arg-Asn-Cys-Trp-Pro-Arg-Val-Arg-Gly-Val-Ala-Met-Asn-Pro-Val	16	335
Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr	16	336
Val-Phe-Arg-Ala-His-Val-Lys-His-Arg-Lys-Gly-Ala-Ala-Arg-Leu	15	337
Pro-Gly-Arg-Gly-Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro	15	338
Ala-Pro-Leu-Ala-Lys-Val-Val-Phe-Arg-Asp-Pro-Tyr-Arg-Phe-Lys	15	339
Arg-Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala	15	340
Val-Lys-Leu-Pro-Ser-Gly-Ser-Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn	15	341
Lys-Lys-Val-Ile-Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val	15	342
Ser-Ser-Ala-Asn-Arg-Ala-Val-Val-Gly-Val-Val-Ala-Gly-Gly-Gly	15	343
Val-Ala-Gly-Gly-Gly-Arg-Ile-Asp-Lys-Pro-Ile-Leu-Lys-Ala-Gly	15	344
Leu-Lys-Ala-Gly-Arg-Ala-Tyr-His-Lys-Tyr-Lys-Ala-Lys-Arg-Asn	15	345
His-Ile-Gly-Lys-Pro-Ser-Thr-Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly	15	346
Ile-Arg-Arg-Asp-Ala-Pro-Ala-Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala	15	347
Gly-Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu	15	348
Arg-Lys-Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg	15	349

Having demonstrated the identification of a melanoma tumor antigen using the instant method, one of skill in the art can readily appreciate the broad application of the instant screening method for identifying MHC class II-dependent tumor-associated T helper cell antigens for other cancers as well as infectious agents. In contrast to the conventional cDNA library-Ii fusion approach (Wang (2001) *supra*), the instant method advantageously does not require prior knowledge of the MHC class II restriction element as

proteins expressed from tumor cDNA libraries are presented to T helper cells by MHC class II-positive B cells, wherein the antigenic regions of said proteins have been naturally processed by APCs. Further, instead of the lysogenic filamentous phage commonly used in phage display libraries, lytic phage were employed. Advantages for using lytic phage such as T7 include the fact that the cDNA is located at the 3' end of protein 10B, requiring only one correct reading frame fusion, whereas in filamentous phage the cDNA is located in the middle of pIII, thus requiring two in-frame fusions; and the lytic life cycle of T7 phage avoids negative selection of proteins during protein transport through the bacterial membrane, which is necessary for assembling filamentous phage.

As used in the context of the present invention, Major Histocompatibility Complex (MHC) is a generic designation meant to encompass the histo-compatibility antigen systems described in different species, including the human leukocyte antigens (HLA). In contrast to MHC class I, MHC class II molecules are found on B cells, macrophages and other antigen presenting cells, collectively referred to herein as MHC class II-positive APCs. MHC class II-positive APCs facilitate the elicitation of an immune response to an antigen by presenting the antigen to T helper cells. Such antigens are designated herein as being MHC class II-dependent. MHC class II-dependent antigens of particular interest in the present invention are disease-associated antigens including tumor-associated and infectious agent-associated antigens. In certain embodiments, a disease-associated antigen is a protein or peptide unique to a tumor cell or infectious agent which can elicit an immune response in a subject, including a cellular or humoral immune response.

The instant method finds application in the identification of tumor-associated antigens from cancers including, but not limited to, melanomas, metastases, adenocarcinoma, thymoma, lymphoma, sarcoma, lung cancer, liver cancer, colon cancer, non-Hodgkins lymphoma, Hodgkins lymphoma, leukemias, uterine cancer, breast cancer, prostate cancer, ovarian cancer, cervical cancer, bladder cancer, kidney cancer, pancreatic cancer and others.

Examples of infectious agents for which MHC class II-dependent antigens can be identified include, but are not limited to, viruses such Hepadnaviridae including hepatitis B virus (HBV); Flaviviridae including human hepatitis C virus (HCV), yellow fever virus and dengue viruses; Retroviridae including human immunodeficiency viruses (HIV) and human T lymphotropic viruses (HTLV1 and HTLV2); Herpesviridae including herpes simplex viruses (HSV-1 and HSV-2), Epstein Barr virus (EBV), cytomegalovirus, varicella-zoster virus (VZV), human herpes virus 6 (HHV-6) human herpes virus 8 (HHV-8), and herpes B virus; Papovaviridae including human papilloma viruses; Rhabdoviridae including rabies virus; Paramyxoviridae including respiratory syncytial virus; Reoviridae including rotaviruses; Bunyaviridae including hantaviruses; Filoviridae including Ebola virus; Adenoviridae; Parvoviridae including parvovirus B-19; Arenaviridae including Lassa virus; Orthomyxoviridae including influenza viruses; Poxviridae including Orf virus and Monkey pox virus; Togaviridae; Coronaviridae including corona viruses; and Picornaviridae.

Non-viral infectious agents include, *e.g.*, pathogenic protozoa such as *Pneumocystis carinii*, *Trypanosoma*, *Leishmania*, *Plasmodia*, and *Toxoplasma gondii*; bacteria such as Mycobacteria, and Legioniella; and fungi such as *Histoplasma capsulatum* and *Coccidioides immitis*.

MHC class II-dependent disease-associated antigens are identified in accordance with the present invention by expressing a library of disease-derived proteins in lytic bacteriophage for subsequent presentation by antigen presenting cells to T helper cells. The term "library of disease-derived proteins", when used in the context of the present invention, is intended to mean a collection of proteins obtained from or originating from a tumor cell or infectious agent. Included within the library of disease-derived proteins are general structural proteins and enzymes as well as disease-associated antigens.

Expression and display of the library of disease-derived proteins in lytic bacteriophage can be carried out using conventional cDNA or genomic phage display library construction methods with insertion of the cDNA or genomic library into commercially available lytic bacteriophage for expression and display on the surface of the phage. The cloned cDNA or gene can encode a complete protein or portions thereof. Methods for library construction are well-known in the art and can be found in general laboratory manuals such as Ausebel et al. (Eds) (1991) *Current Protocols in Molecular Biology*, New York; Greene Publishing & Wiley-Interscience; Sambrook, J. et al. (1989) *Molecular Cloning: A Laboratory Manual* (2nd ed.) Cold Spring Harbor: Cold Spring Harbor Laboratory Press.

Lytic bacteriophage are phage that lyse a host cell after the initial infection in order to release new phage particles. Lytic bacteriophage include lambda-phage, T3-phage, T4-phage, TB7-phage and T7-phage. Lytic bacteriophage vectors, such as lambda, T4 and T7 are of practical use since they are independent of *E. coli* secretion. Bacteriophage vectors are well-known in the art and commercially available. Examples of commercial T7 bacteriophage vectors include the

T7SELECT series of vectors for engineering and packaging of DNA into T7 phage particles (NOVAGEN, Madison, WI). See also U.S. Patent Nos. 5,223,409; 5,403,484; 5,571,698 and 5,766,905.

The library of phage can be used directly in the instant library screen, or alternatively amplified using an appropriate host (*e.g., E. coli*). The library of phage displaying the disease-derived proteins is subsequently assessed for the presence of disease-associated antigens by pulsing or contacting antigen presenting cells with the library of phage and detecting or measuring T cell responses during co-incubation of the antigen presenting cells and T helper cells. Advantageously, the antigen presenting cells naturally process and display disease-derived proteins on their surface so that those antigen presenting cells which present disease-associated antigens can be recognized by T helper cells. Examples of antigen presenting cells that can be used include, but are not limited to, antigen presenting cells such as EBV transformed B cell lines (Topalian, et al. (1994) *Int. J. Cancer* 58:69-79), monocytes and dendritic cells, and synthetic APC (see, *e.g.*, U.S. Patent No. 6,355,479).

Any conventional method can be employed to determine whether an antigen presenting cell is presenting an MHC class II-dependent disease-associated antigen which is recognized by a T helper cell. Such methods can be qualitative or quantitative to determine the degree of T helper cell recognition or stimulation. Exemplary methods include, but are not limited to, ^{51}CR release cytotoxicity assays (Cerundolo, et al. (1990) *Nature* 345:449-452.); cytokine secretion assays such as γ-IFN, GM-CSF or TNF secretion (Schwartzentruber, et al. (1991) *J. Immunology* 146:3674-3681); or proliferation assays (*e.g.*, a BrdU assay). A T

helper cell which is stimulated (*e.g.*, exhibits an increase in proliferation) in the presence of an APC is indicative of the presence of an MHC class II-dependent disease-associated antigen on the surface of said APC.

An MHC class II-dependent disease-associated antigen or epitope peptide thereof identified using the method of present invention finds application in the preparation of a vaccine for preventing or treating the disease associated with said antigen (*i.e.*, cancer or infectious disease) as well as in the diagnosis of said disease or in the production of antibodies for treatment or diagnosis. Moreover, it is contemplated that the antigen presenting cells which presents the MHC class II-dependent disease-associated antigen can also be used in the preparation of a vaccine or in the production of antibodies.

For use in vaccines, diagnosis or antibody production, it is contemplated that the entire disease-associated antigen can be used or, alternatively, an immunogenic peptide or peptide epitope of said antigen can be used. An immunogenic peptide or peptide epitope is a peptide that contains an allele-specific motif or supermotif such that the peptide will bind an HLA molecule and induce a cellular or humoral immune response. Thus, immunogenic peptides of the invention are capable of binding to an appropriate HLA molecule and thereafter inducing a cytotoxic T lymphocyte (CTL) response, or a helper T lymphocyte (HTL) response, to the peptide.

An epitope is the collective features of a molecule, such as primary, secondary and tertiary peptide structure, and charge, that together form a site recognized by an immunoglobulin, T cell receptor or HLA molecule. Alternatively, an epitope can be defined as a set of amino acid residues which is involved in recognition by a particular immunoglobulin, or in the context of T cells,

those residues necessary for recognition by T cell receptor proteins and/or Major Histocompatibility Complex (MHC) receptors. Epitopes can be isolated, purified or otherwise prepared/derived by humans. For example, epitopes can be prepared by isolation from a natural source, or they can be synthesized in accordance with standard protocols in the art. Synthetic epitopes can contain artificial amino acids, *i.e.*, amino acid mimetics, such as D isomers of natural occurring L amino acids or non-natural amino acids such as cyclohexylalanine. Throughout this disclosure, the terms epitope and peptide are often used interchangeably.

Immunogenic peptides or peptide epitopes of the invention can be readily identified using conventional methods. For example, web-based algorithms can be used to analyze the amino acid sequence of a disease-associated antigen for potential human MHC class II binding epitopes. An exemplary algorithm is SYFPEITHI (Rammensee, et al. (1999) *Immunogenetics* 50:213) which ranks peptides according to a score taking into account the presence of primary and secondary MHC-binding anchor residues. Another exemplary algorithm is BIMAS (Parker, et al. (1994) *J. Immunol.* 152:163) which ranks potential binding according to the predicted half-time of dissociation of peptide/MHC complexes. Exemplary immunogenic peptides of RPL8 are disclosed in Table 3 and include SEQ ID NOs:5-249.

For use in accordance with the compositions and methods disclosed herein, a disease-associated antigen or immunogenic peptide thereof can be recombinantly-produced or chemically-synthesized using conventional methods well-known to the skilled artisan.

In general, recombinant production of a protein or peptide requires incorporation of nucleic acid sequences encoding said protein or peptide into a recombinant

expression vector in a form suitable for expression of the protein or peptide in a host cell. A suitable form for expression provides that the recombinant expression vector includes one or more regulatory sequences operatively-linked to the nucleic acids encoding the protein or peptide in a manner which allows for transcription of the nucleic acids into mRNA and translation of the mRNA into the protein. Regulatory sequences can include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are known to those skilled in the art and are described in Goeddel D.D., ed., Gene Expression Technology, Academic Press, San Diego, CA (1991). It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transfected and/or the level of expression required. Nucleic acid sequences or expression vectors harboring nucleic acid sequences encoding a disease-associated antigen or peptide can be introduced into a host cell, which may be of eukaryotic or prokaryotic origin, by standard techniques for transforming cells. Suitable methods for transforming host cells can be found in Sambrook, *et al.* (Molecular Cloning: A Laboratory Manual, 3rd Edition, Cold Spring Harbor Laboratory Press (2000)) and other laboratory manuals. The number of host cells transformed with a nucleic acid sequence will depend, at least in part, upon the type of recombinant expression vector used and the type of transformation technique used. Nucleic acids can be introduced into a host cell transiently, or more typically, for long-term expression the nucleic acid sequence is stably integrated into the genome of the host cell or remains as a stable episome in the host cell. Once produced, a disease-associated antigen or peptide can be recovered from culture medium as a secreted polypeptide, although it also may be

recovered from host cell lysates when directly expressed without a secretory signal. When a disease-associated antigen or immunogenic peptide is expressed in a recombinant cell other than one of human origin, the disease-associated antigen or immunogenic peptide is substantially free of proteins or polypeptides of human origin. However, it may be necessary to purify the disease-associated antigen or peptide from recombinant cell proteins or polypeptides using conventional protein purification methods to obtain preparations that are substantially homogeneous as to the disease-associated antigen or immunogenic peptide.

In addition to recombinant production, a disease-associated antigen or immunogenic peptide may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer, Boston, MA). Various fragments of disease-associated antigen or immunogenic peptide can be chemically-synthesized separately and combined using chemical methods to produce a full-length molecule.

Whether recombinantly-produced or chemically-synthesized, a disease-associated antigen or immunogenic peptide can be further modified prior to use. For example, the peptides may be glycosylated, phosphorylated or fluorescently-tagged using well-known methods.

Disease-associated antigens or immunogenic peptides of the invention are useful for inducing an immune response to tumor cells or infectious agents. Accordingly, an MHC class II-dependent disease-associated T helper cell antigen of the present invention, or immunogenic peptide thereof, can be used as a vaccine either prophylactically or therapeutically.

When provided prophylactically the vaccine is provided in advance of any evidence of disease. The prophylactic administration of the disease-associated antigen or immunogenic peptide vaccine should be administered as an effective amount to prevent or attenuate disease in a mammal. In one embodiment, mammals (*e.g.*, humans, zoological animals, companion animals or livestock), at high risk for disease are prophylactically treated with the vaccines of this invention. Examples of such mammals include, but are not limited to, subjects with a family history of disease (*e.g.*, genetically predisposed to cancer), subjects at risk of having a disease (*e.g.*, individuals who have been exposed to cancer causing or infectious agents), subjects afflicted with a disease which has been treated and are therefore at risk for reoccurrence. When provided therapeutically, the vaccine is provided to enhance the subject's own immune response to the disease-associated antigen. The vaccine, which acts as an immunogen, can be a cell expressing the antigen or immunogic peptide (*e.g.*, an APC as presented herein), cell lysate from cells transfected with a recombinant expression vector encoding the antigen or immunogic peptide, cell lysates from cells transfected with a recombinant expression vector encoding for the antigen or immunogic peptide, or a culture supernatant containing the expressed the antigen or immunogic peptide. Alternatively, the immunogen is a partially or substantially purified recombinant protein, peptide or analog thereof encoding for an antigen. The antigen or immunogic peptide can be conjugated with lipoprotein or administered in liposomal form or with adjuvant using conventional methodologies. As will be appreciated by the skilled artisan, a subject having, at risk of having, or suspected of having a disease will be administered a disease-associated antigen or immunogenic peptide for the disease being prevented or treated. By way of

illustration, the instant RPL8 protein (SEQ ID NO:1) or immunogenic fragment or peptide thereof (*e.g.*, SEQ ID NO:3 and SEQ ID NOs:5-249) is useful in the prevention or treatment of melanoma, glioma and ovarian cancer.

An effective amount of a disease-associated antigen or immunogenic peptide which can be used in accordance with the method of the invention is an amount which prevents, eliminates, alleviates, or reduces at least one sign or symptom of a cancer or infectious disease. For example, signs or symptoms associated with a cancer that can be monitored to determine the effectiveness of a tumor-associated antigen include, but are not limited to, tumor size and anti-tumor-associated antigen antibody production. Similarly, effectiveness of an infectious agent-associated antigen can be detected by monitoring antibody titer to the specific infectious agent-associated antigen. The amount of the disease-associated antigen or immunogenic peptide required to achieve the desired outcome of preventing, eliminating, alleviating or reducing a sign or symptom of disease will be dependent on the pharmaceutical composition employed, the patient and the condition of the patient, the mode of administration, and the type of disease being prevented or treated. Dose optimization is routine in the art and can be determined by the skilled clinician.

The disease-associated antigen or immunogenic peptide, which may be used alone or in combination, can be administered to a subject in need thereof, using any of the standard types of administration, such as intravenous, intradermal, subcutaneous, oral, rectal, and transdermal administration. Standard pharmaceutical carriers, adjuvants, such as saponins, GM-CSF, and interleukins and so forth can also be used. A generally recognized compendium of methods and ingredients of pharmaceutical compositions is Remington:

The Science and Practice of Pharmacy, Alfonso R. Gennaro, editor, 20th ed. Lippincott Williams & Wilkins: Philadelphia, PA, 2000. Further, proteins and peptides can be formulated into vaccines, as can dendritic cells, or other cells which present relevant MHC/peptide complexes. These proteins and peptides can also be used to form multimeric complexes of HLA/peptides, such as those described by Dunbar, et al. (1998) *Curr. Biol.* 8:413-416, wherein four peptide/MHC/biotin complexes are attached to a streptavidin or avidin molecule. Such complexes can be used to identify and/or to stimulate T cell precursors.

Similarly, the invention contemplates therapies wherein the nucleic acid molecule which encodes either full-length disease-associated antigen, or one or more of the relevant immunogenic peptides, in polytope form, is incorporated into a vector, such as an adenovirus-based vector, to render it transfectable into eukaryotic cells, such as human cells.

It is contemplated that a disease-associated antigen or immunogenic peptide can be conjugated to other species. The other species comprehended include all chemical species which can be fused to the protein or peptide without affecting the binding of the protein or peptide by T cells. Specific examples are, for example, other antigens such as epitopes which can elicit a separate immune response, carrier molecules which aid in absorption or protect the protein or peptide from enzyme action in order to improve the effective half-life.

As indicated, the invention involves, *inter alia*, an immune response to a disease-associated antigen or immunogenic peptide of interest. One ramification of this is the ability to monitor the course of a therapy. In this regard, a subject in need of the therapy receives a vaccination of a type described herein. Such a vaccination

results, *e.g.*, in a T cell response against cells presenting MHC/peptide complexes on their cells. The response also includes an antibody response, possibly a result of the release of antibody provoking proteins via the lysis of cells by the T cells. Hence, one can monitor the effect of a vaccine, by monitoring an immune response. As is indicated, *supra*, an increase in antibody titer or T cell count may be taken as an indicia of progress with a vaccine, and vice versa. The effects of a vaccine can also be measured by monitoring the T cell response of the subject receiving the vaccine. A number of assays can be used to measure the precursor frequency of these stimulated T cells. These include, but are not limited to, chromium release assays, TNF release assays, IFNγ release assays, an ELISPOT assay, and so forth. Changes in precursor T cell frequencies can be measured and correlated to the efficacy of the vaccine.

In addition to a disease-associated antigen or immunogenic peptide, a therapeutic of the invention also includes an antibody or antibodies reactive with a MHC class II-dependent disease-associated antigen or epitope peptide. In some embodiments, an antibody of the invention is raised against an antigen or epitope peptide identified by the instant screening method. In another embodiment, an antibody of the invention specifically binds an antigen or epitope peptide identified by the instant screening method. Such antibodies can be monoclonal and polyclonal and are made by conventional methods known to those skilled in the art. See, *e.g.*, Current Protocols in Immunology, Wiley/Greene, NY; and Antibodies A Laboratory Manual Harlow, Harlow and Lane, Cold Spring Harbor Laboratory Press, 1989. Moreover, such antibodies can be natural or partially or wholly synthetically produced. All fragments or derivatives thereof which maintain the ability to specifically bind to a MHC

class II-dependent disease-associated antigen are also included. The antibodies can be a member of any immunoglobulin class, including any of the human classes: IgG, IgM, IgA, IgD, and IgE.

Antibody fragments can be any derivative of an antibody which is less than full-length. In general, an antibody fragment retains at least a significant portion of the full-length antibody's specific binding ability. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, scFv, Fv, diabody, or Fd fragments. The antibody fragment can be produced by any means. For instance, the antibody fragment can be enzymatically or chemically produced by fragmentation of an intact antibody or it can be recombinantly produced from a gene encoding the partial antibody sequence. The antibody fragment can optionally be a single-chain antibody fragment. Alternatively, the fragment can be multiple chains which are linked together, for instance, by disulfide linkages. The fragment can also optionally be a multi-molecular complex. A functional antibody fragment typically contains at least about 50 amino acids and more typically contains at least about 200 amino acids.

An antibody for use in the methods of the present invention can be generated using classical cloning and cell fusion techniques. For example, the antigen or epitope peptide of interest is typically administered (*e.g.*, intraperitoneal injection) to wild-type or inbred mice (*e.g.*, BALB/c) or transgenic mice which produce desired antibodies, or rats, rabbits or other animal species which can produce native or human antibodies. The antigen or epitope peptide can be administered alone, or mixed with adjuvant, or expressed from a vector (VEE replicon vector), or as DNA, or as a fusion protein to induce an immune response. Fusion

proteins contain the antigen or epitope peptide against which an immune response is desired coupled to carrier proteins, such as histidine tag (his), mouse IgG2a Fc domain, β-galactosidase, glutathione S-transferase, keyhole limpet hemocyanin (KLH), or bovine serum albumin, to name a few. In these cases, the peptides serve as haptens with the carrier proteins. After the animal is boosted, for example, two or more times, the spleen is removed and splenocytes are extracted and fused with myeloma cells using the well-known processes (Kohler and Milstein (1975) *Nature* 256:495-497; Harlow and Lane (1988) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York). The resulting hybrid cells are then cloned in the conventional manner, *e.g.*, using limiting dilution, and the resulting clones, which produce the desired monoclonal antibodies, are cultured.

Alternatively, antibodies which specifically bind a MHC class II-dependent disease-associated antigen or epitope peptide are produced by a phage display method. Methods of producing phage display antibodies are well-known in the art (*e.g.*, Huse, et al. (1989) *Science* 246(4935):1275-81).

Selection of an antibody specific for a MHC class II-dependent disease-associated antigen or epitope peptide is based on binding affinity and can be determined by various well-known immunoassays including, enzyme-linked immunosorbent, immunodiffusion chemiluminescent, immunofluorescent, immunohistochemical, radioimmunoassay, agglutination, complement fixation, immunoelectrophoresis, and immunoprecipitation assays and the like which can be performed *in vitro*, *in vivo* or *in situ*. Such standard techniques are well-known to those of skill in the art (see, *e.g.*, "Methods in Immunodiagnosis", 2nd Edition, Rose and Bigazzi, eds. John Wiley & Sons, 1980; Campbell et al., "Methods and Immunology", W.A. Benjamin, Inc., 1964; and

Oellerich, M. (1984) *J. Clin. Chem. Clin. Biochem.* 22:895-904).

As with a MHC class II-dependent disease-associated antigen or epitope peptide, prevention or treatment with an antibody generally involves administering an effective amount of the antibody or antibody fragment to a subject in need of such treatment so that signs or symptoms associated with the disease are alleviated, prevented, or ameliorated. To produce an antibody which is more compatible with human vaccination, humanized chimeric antibodies may be desirable (see Morrison (1985) *Science* 229:1202; Oi, et al. (1986) *Biotechniques* 4:214).

Antibodies of the invention are also useful in diagnostic, prognostic, or predictive methods to detect the presence of diseased tissues (*e.g.*, tumors or infectious agents) via techniques such as ELISA, western blotting, or immunohistochemistry. The general method for detecting such an antigen provides contacting a sample with an antibody which specifically binds the antigen, so that an antibody-antigen complex is formed and detecting the antibody-antigen complex using any one of the immunoassays described above as well a number of well-known immunoassays used to detect and/or quantitate antigens (see, for example, Harlow and Lane (1988) *supra*). Such well-known immunoassays include antibody capture assays, antigen capture assays, and two-antibody sandwich assays.

Immunoassays typically rely on labeled antigens, antibodies, or secondary reagents for detection. These proteins may be labeled with radioactive compounds, enzymes, biotin, or fluorochromes. Of these, radioactive labeling can be used for almost all types of assays. Enzyme-conjugated labels are particularly useful when radioactivity must be avoided or when quick results are needed. Biotin-coupled

reagents usually are detected with labeled streptavidin. Streptavidin binds tightly and quickly to biotin and may be labeled with radioisotopes or enzymes. Fluorochromes, although requiring expensive equipment for their use, provide a very sensitive method of detection. Those of ordinary skill in the art will know of other suitable labels which can be employed in accordance with the present invention. The binding of these labels to antibodies or fragments thereof can be accomplished using standard techniques (*e.g.*, Kennedy, et al. (1976) *Clin. Chim. Acta* 70:1-31; Schurs, et al. (1977) *Clin. Chim Acta* 81:1-40) and methods of detecting these labels are also well-known to the skilled artisan.

Antibodies disclosed herein can also be used for targeting therapeutic agents to cells expressing MHC class II-dependent disease-associated antigen. In this embodiment, therapeutic agents such as anti-neoplastic, anti-viral, anti-bacterial, or anti-fungal agents are operably linked to an antibody of the invention to facilitate targeting of the therapeutic agent to the target cell.

The invention is described in greater detail by the following non-limiting examples.

Example 1: Melanoma Patients

Melanoma patients #3472, 3507, 3522, 3523, and 3533 had metastatic lesions excised between 1 and 3 years ago. Patient 35 had a "low risk" primary melanoma of the superficial spreading type excised. The tumor was 0.69 mm in thickness and had a brisk lymphocytic infiltrate (Clark, et al. (1989) *J. Natl. Cancer Inst.* 81:1893-904). The primary lesion was excised approximately 23 years ago and there was no recurrence or metastasis since. PBMC were obtained from the patients' peripheral blood on the day of surgery (3522, 3523) or as late as 4 months after surgery (3507) with informed

consent and under an approved protocol.

Example 2: Materials

Cell lines. Melanoma cell line WM35 was established from a primary melanoma (Satyamoorthy, et al. (1997) *Melanoma Res.* 7(Suppl 2):S35-42) and maintained in MCDB153-L15 medium (SIGMA-ALDRICH, St. Louis, MO) containing 2% fetal bovine serum (FBS). EBV-B35 was established from freshly isolated PBMC of patient 35 using 2.5 transforming U/cell of B95-8 virus according to known methods (Somasundaram, et al. (2003) *supra*). The cell line was maintained in RPMI 1640 medium with GLUTAMAX (GIBCO-INVITROGEN, Carlsbad, CA) supplemented with 10% FBS.

Th35-1A helper T cell clone was established by co-culturing PBMC with the autologous WM35 melanoma cell line, both derived from patient 35 (Somasundaram, et al. (2003) *supra*). COS-7L cells (GIBCO-INVITROGEN) were maintained in Dulbecco's Modification of Eagle's Medium (DMEM; GIBCO-INVITROGEN) supplemented with 10% FBS.

Antibodies. Anti-HLA class II antibody B33.1 is known in the art (Loza & Perussia (2001) *Nature Immunology* 2:917-924) and normal mouse IgG was obtained from Cappel-ICN (Costa Mesa, CA).

Example 3: cDNA Library Construction and Screening

EBV-B cells have been shown to present to T helper cells a tetanus toxoid cDNA fragment expressed by lysogenic filamentous phage (Somasundaram, et al. (2004) *Clin. Exp. Immunol.* 135:247-52). This approach was modified herein by using lytic bacteriophase (Rosenberg, et al. (1996) *inNovations* 6:1-6) to express a melanoma cDNA library. Messenger RNA was isolated from cultured WM35 cells using the FASTTRACK® 2.0 kit (INVITROGEN, Carlsbad, CA). Four μg of

polyA$^+$ RNA were converted to cDNA using the ORIENTEXPRESS system (EMD Biosciences NOVAGEN, San Diego, CA) and ligated into T7SELECT10-3b vector (EMD Biosciences NOVAGEN) according to the manufacturer's instructions. The ligated DNA was packed *in vitro* using T7 packing extract (library size was 3.2×10^6 independent phage). The library was plate-amplified once in BLT5615 *E. coli* cells (EMD Biosciences NOVAGEN) and divided into 100 phage/pool. For screening, each pool was amplified once in liquid culture, and released phage were purified twice by PEG/NaCl precipitation. Phage titers were determined, and 3000 pfu were used to pulse EBV-B35 cells for co-culturing with Th35-1A cells in lymphocyte proliferation and interferon-γ release assays. Phage from one pool stimulated proliferation and interferon-γ release in Th35-1A cells.

Example 4: Assays

Lymphocyte Proliferation Assay. The lymphocyte proliferation assay was performed according to standard methods (Somasundaram, et al. (1995) *J. Immunol.* 155:3253-61). For screening of Th35-1A cell-reactivity with phage libraries, T helper cells ($1-2 \times 10^4$/well of 96-well round-bottom microtiter plates; CORNING, Corning, NY) were cultured with irradiated autologous EBV-B cells (10^4/well) pre-pulsed with $1-3 \times 10^3$ phage. To determine T helper or PBMC reactivity with peptide, adherent monocytes (5×10^4/well, obtained from PBMC) pre-pulsed with various concentrations (3.1-50 μM) of peptide were incubated with Th35-1A cells or PBMC (5×10^4/well). T helper cells or PBMC were stimulated with peptide-pulsed monocytes once or twice. All incubations were at 37°C for 5 days in RPMI 1640/GLUTAMAX medium supplemented with 10% heat-inactivated human AB serum (Gemini Bioproducts, West Sacramento, CA), 10 mM HEPES and 5×10^{-5} M

2-mercaptoethanol (both from SIGMA-ALDRICH). Proliferative responses of lymphocytes were determined using a standard [^{3}H]-thymidine incorporation assay. All determinations were performed in triplicate. Results are expressed as counts per minute (cpm) incorporated into lymphocytes. The lymphocyte proliferation inhibition assay with anti-HLA class II antibody B33.1 was performed using established methods (Somasundaram, et al. (1995) *supra*).

IFN-γ Release Assay. Supernatants obtained 48 hours after T helper cell stimulation with phage-pulsed EBV-B cells were tested for the presence of IFN-γ using an ENDOGEN ELISA kit (Pierce Biotechnology, Inc., Rockford, IL).

Example 5: Peptide Design

DNA and deduced amino acid sequence comparisons were performed with the BLAST program provided by the National Center for Biotechnology Information. The amino acid sequence was deduced from the DNA sequence using EXPASY. DRB1*07011 binding epitopes were determined from the deduced amino acid sequence of the isolated cDNA clone by using the SYFPEITHI algorithm and Rammensee epitope prediction model (Rammensee, et al. (1999) *Immunogenetics* 50:213-9) and were limited to epitopes with a binding score >20. Selected peptides were synthesized and HPLC-purified. The following peptides were used: Val-Gly-Leu-Ile-Ala-Ala-Arg-Arg-Thr-Gly-Arg-Leu-Arg-Gly-Thr (SEQ ID NO:2), with a score of 24 (peptide #1, RPL8 position 235-249); Thr-Gly-Arg-Leu-Arg-Gly-Thr-Lys-Thr-Val-Gln-Glu-Lys-Glu-Asn (SEQ ID NO:3), with a score of 24 (peptide #2, RPL8 position 243-257); and Arg-Pro-Gly-Leu-Leu-Gly-Ala-Ser-Val-Leu-Gly-Leu-Asp-Asp-Ile (SEQ ID NO:350) with a score of 22 (control peptide, telomerase reverse transcriptase).

Example 6: Full-Length RPL8 Cloning

The GENERACER™ kit (INVITROGEN) and oligonucleotides based on the cDNA sequence of the phage that stimulated Th35-1A cell proliferation were used to determine the 5′ and 3′ end of RPL8 mRNA in WM35 cells. Both fragments (5′ and 3′ end) were sequenced and oligonucleotides were designed to clone full-length RPL8 cDNA by RT-PCR (SUPERSCRIPT™ III one-step RT-PCR with PLATINUM Taq; INVITROGEN).

Example 7: Northern Blot Analysis

Northern blot analysis of cells for the presence of RPL8 RNA was performed according to standard procedures. In short, total RNA was isolated from cultured cells using MICRO-TO-MIDI total RNA purification system (INVITROGEN). Ten μg of each RNA were separated on a 1.5% formaldehyde agarose gel and transferred onto a nylon membrane by electroblotting. The membrane was probed with [α-^{32}P]-dCTP-labeled, random-primed (REDIPRIME™ II random prime labeling system; Amersham Biosciences, Piscataway, NJ), full-length RPL8 cDNA. RNA levels were compared using a STORM® PHOSPHORIMAGER system (GE Healthcare, Piscataway, NJ). Assumption of equal loading was based on OD reading and ethidium bromide staining signal of ribosomal RNA. There was no correlation between RNA levels and recognition of cell lysates by Th35-1A cells.

Example 8: Statistical Analyses

Differences between experimental and control values were analyzed for significance by Student's 2-sided *t*-test.

What is claimed is:

1. A method for identifying a MHC class II-dependent disease-associated T helper cell antigen comprising expressing a library of disease-derived proteins in lytic bacteriophage; presenting antigens of the library of disease-derived proteins on the surface of MHC class II-positive antigen presenting cells (APC); contacting the APC with T helper cells and determining T helper cell recognition, wherein the recognition by a T helper cells is indicative of said APC presenting a MHC class II-dependent disease-associated T helper cell antigen.

2. A MHC class II-dependent disease-associated T helper cell antigen identified by the method of claim 1.

3. A vaccine comprising the MHC class II-dependent disease-associated T helper cell antigen identified by the method of claim 1.

4. The vaccine of claim 3, wherein the MHC class II-dependent disease-associated T helper cell antigen is a tumor-associated T helper cell antigen.

5. The vaccine of claim 3, wherein the MHC class II-dependent disease-associated T helper cell antigen is an infectious agent-associated T helper cell antigen.

6. A method for inducing an immune response to a MHC class II-dependent disease-associated T helper cell antigen comprising contacting a T helper cell with the MHC class II-dependent disease-associated T helper cell antigen of claim 2 so that an immune response is induced.

7. A method for preventing or treating cancer comprising administering the vaccine of claim 4 to a subject in need thereof so that cancer in the subject is prevented or treated.

8. A method for preventing or treating an infectious disease comprising administering the vaccine of claim 5 to a subject in need thereof so that infectious disease in the subject is prevented or treated.

9. An isolated antibody which specifically binds the MHC class II-dependent disease-associated T helper cell antigen of claim 2 or an epitope peptide thereof.

10. The isolated antibody of claim 9, wherein the MHC class II-dependent disease-associated T helper cell antigen is a tumor-associated T helper cell antigen.

11. The isolated antibody of claim 9, wherein the MHC class II-dependent disease-associated T helper cell antigen is an infectious agent-associated T helper cell antigen.

12. A method for preventing or treating cancer comprising administering the antibody of claim 10 to a subject in need thereof so that cancer in the subject is prevented or treated.

13. A method for preventing or treating an infectious disease comprising administering the antibody of claim 11 to a subject in need thereof so that infectious disease in the subject is prevented or treated.

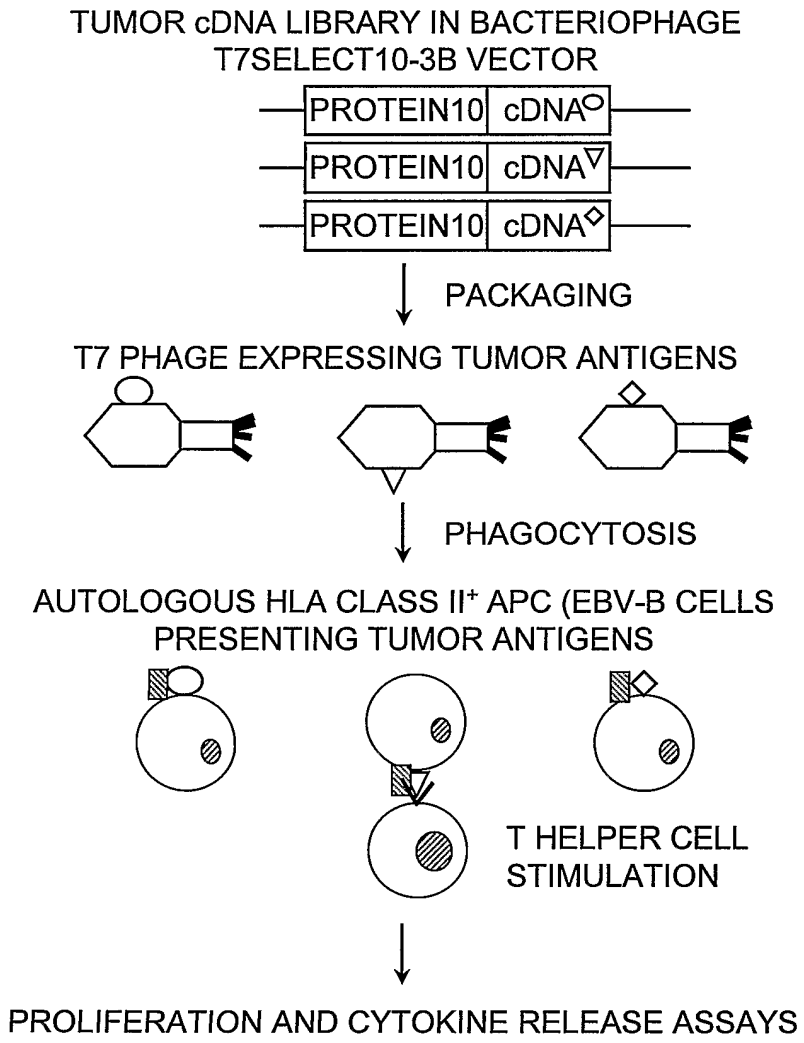

TUMOR cDNA LIBRARY IN BACTERIOPHAGE
T7SELECT10-3B VECTOR
PROTEIN10 cDNA○
PROTEIN10 cDNA▽
PROTEIN10 cDNA◇
PACKAGING
T7 PHAGE EXPRESSING TUMOR ANTIGENS
PHAGOCYTOSIS
AUTOLOGOUS HLA CLASS II+ APC (EBV-B CELLS
PRESENTING TUMOR ANTIGENS
T HELPER CELL
STIMULATION
PROLIFERATION AND CYTOKINE RELEASE ASSAYS

FIG. 1A

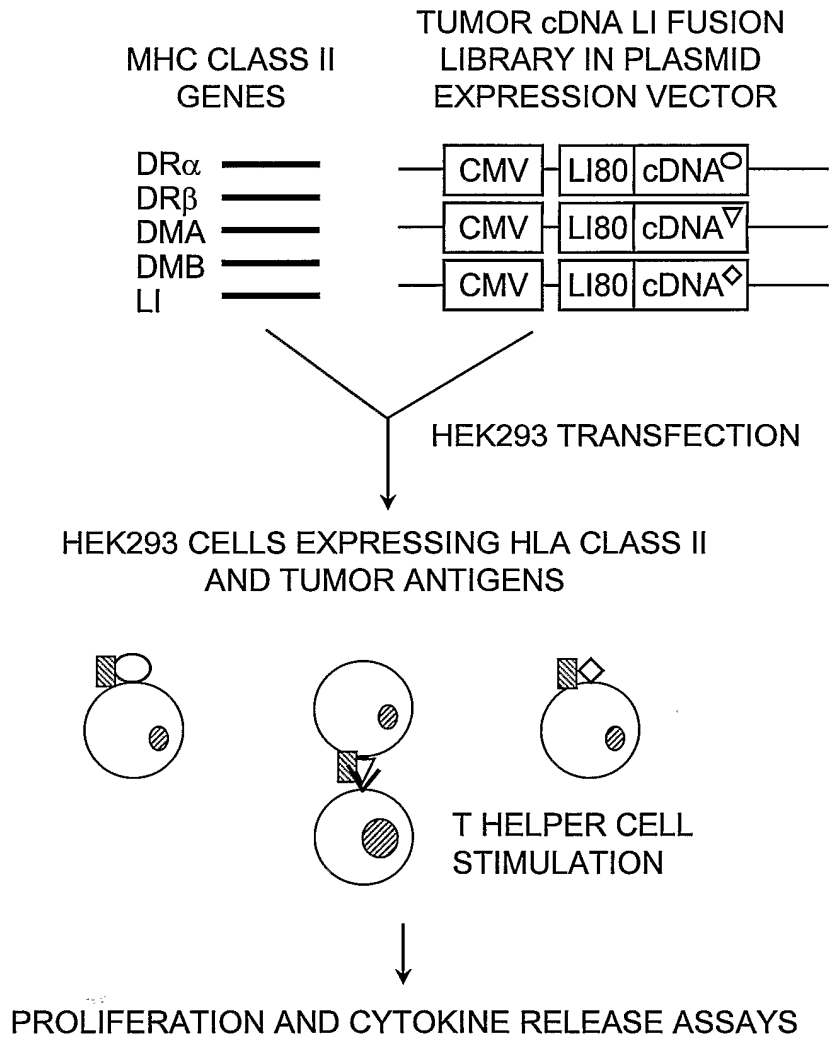

MHC CLASS II
GENES
DRα
DRβ
DMA
DMB
LI
TUMOR cDNA LI FUSION
LIBRARY IN PLASMID
EXPRESSION VECTOR
CMV LI80 cDNA○
CMV LI80 cDNA▽
CMV LI80 cDNA◇
HEK293 TRANSFECTION
HEK293 CELLS EXPRESSING HLA CLASS II
AND TUMOR ANTIGENS
T HELPER CELL
STIMULATION
PROLIFERATION AND CYTOKINE RELEASE ASSAYS

FIG. 1B

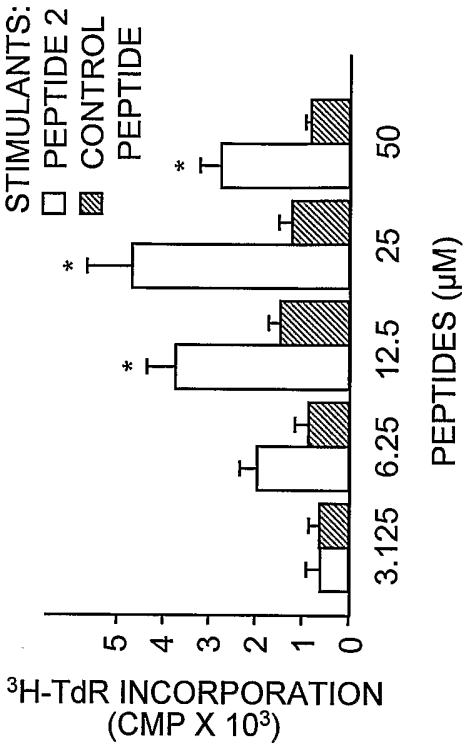


FIG. 2B

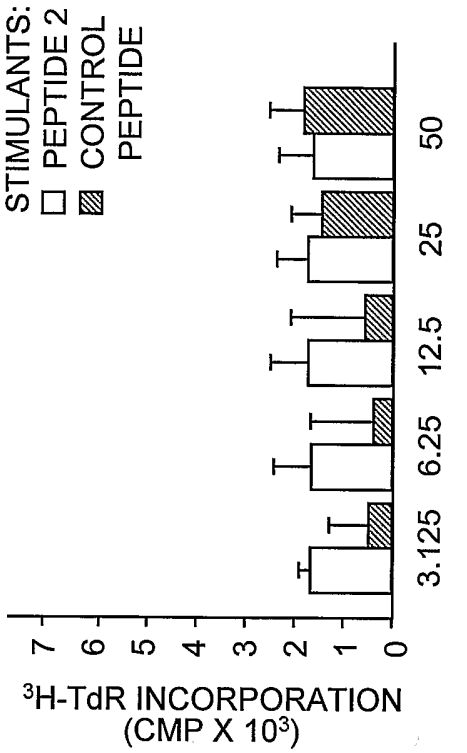


FIG. 2D

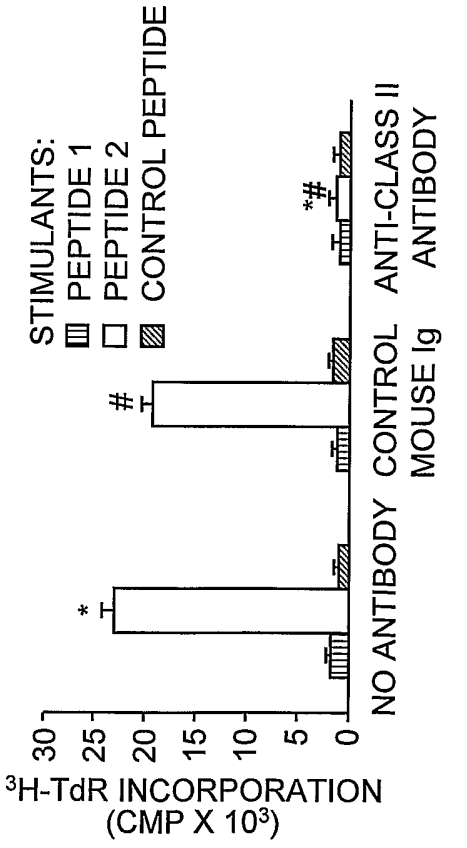


FIG. 2A

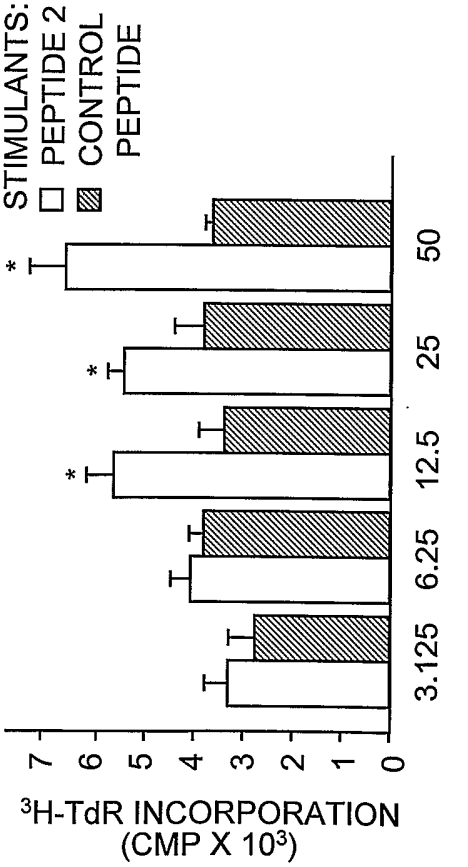


FIG. 2C

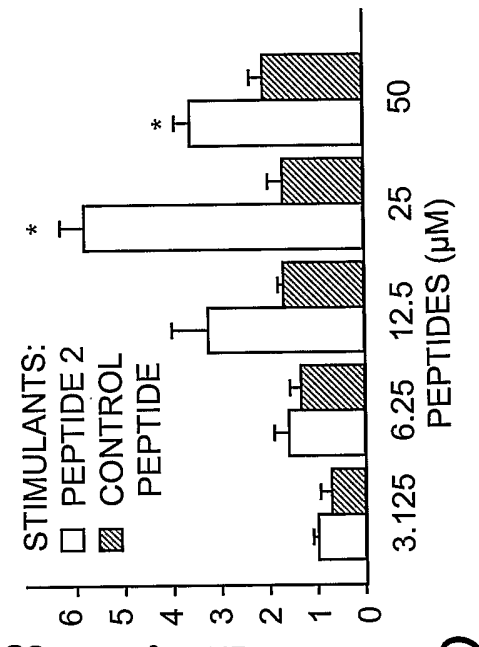


FIG. 3B



FIG. 3D

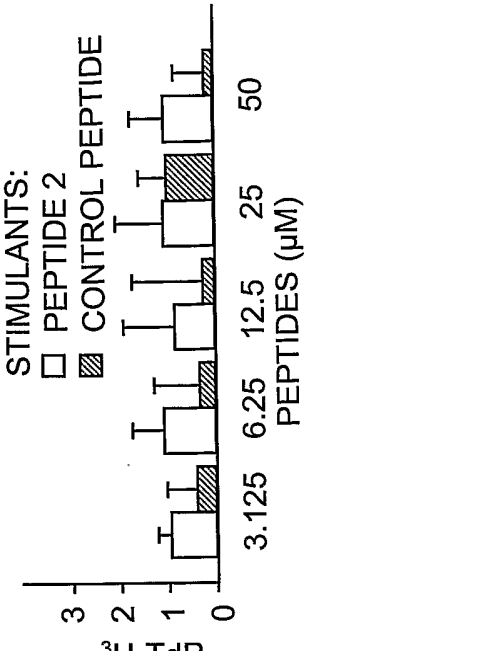


FIG. 3F

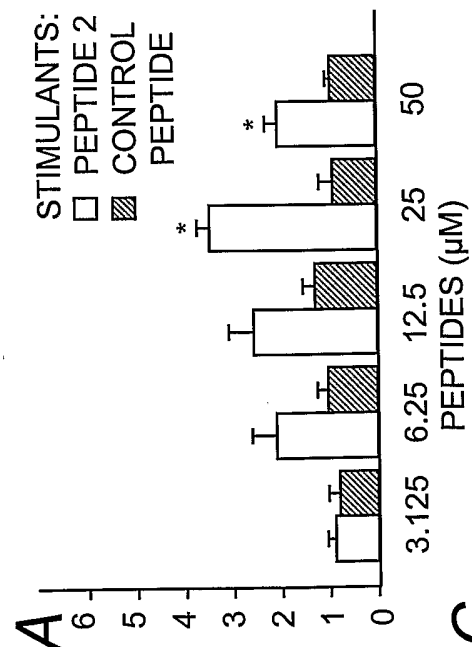


FIG. 3A



FIG. 3C

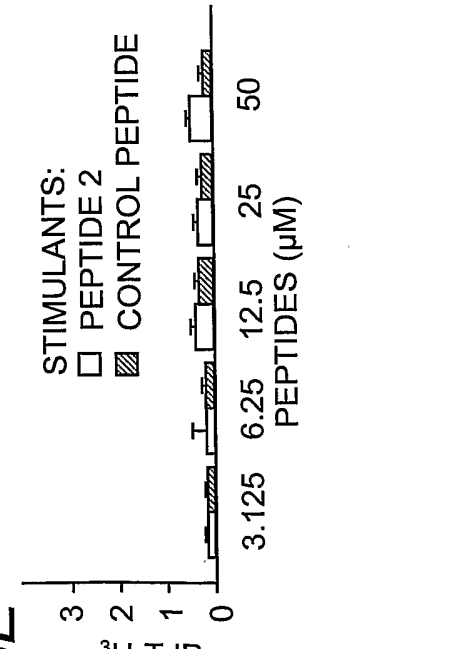


FIG. 3E

SEQUENCE LISTING

<110> The Wistar Institute
Herlyn, Dorothee
Somasundaram, Rajasekharan
Swoboda, Rolf K.

<120> METHOD FOR IDENTIFYING A MHC CLASS II-DEPENDENT TUMOR-ASSOCIATED T HELPER CELL ANTIGEN

<130> WSTR-0032B

<150> US 60/691,029
<151> 2005-06-16

<160> 350

<170> PatentIn version 3.3

<210> 1
<211> 257
<212> PRT
<213> Homo sapiens

<400> 1

Met Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe
1 5 10 15

Arg Ala His Val Lys His Arg Lys Gly Ala Ala Arg Leu Arg Ala Val
20 25 30

Asp Phe Ala Glu Arg His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile
35 40 45

Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys Val Val Phe Arg
50 55 60

Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala Ala Glu
65 70 75 80

Gly Ile His Thr Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu
85 90 95

Asn Val Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile
100 105 110

Val Cys Cys Leu Glu Glu Lys Pro Gly Asp Arg Gly Lys Leu Ala Arg
115 120 125

Ala Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys
130 135 140

```
Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser
145                 150                 155                 160

Ala Asn Arg Ala Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp
                165                 170                 175

Lys Pro Ile Leu Lys Ala Gly Arg Ala Tyr His Lys Tyr Lys Ala Lys
            180                 185                 190

Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val Glu
        195                 200                 205

His Pro Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro Ser Thr
    210                 215                 220

Ile Arg Arg Asp Ala Pro Ala Gly Arg Lys Val Gly Leu Ile Ala Ala
225                 230                 235                 240

Arg Arg Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys Glu
                245                 250                 255

Asn
```

<210> 2
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2

```
Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr
1               5                   10                  15
```

<210> 3
<211> 15
<212> PRT
<213> Homo sapiens

<400> 3

```
Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys Glu Asn
1               5                   10                  15
```

<210> 4
<211> 967
<212> DNA
<213> Homo sapiens

<400> 4
gcggcatggg cagtatccgc cgccatcctc ttccgtgagg cgcgctgaga cccggaccgg 60

ccctcctgag aggatgccgg tgcgggcgcc cgcggagagg gacccgtcgc catgggccgt 120

gtgatccgtg gacagaggaa gggcgccggg tctgtgttcc gcgcgcacgt gaagcaccgt 180

aaaggcgctg cgcgcctgcg cgccgtggat ttcgctgagc ggcacggcta catcaagggc 240

atcgtcaagg acatcatcca cgacccgggc cgcggcgcgc ccctcgccaa ggtggtcttc 300

cgggatccgt atcggtttaa gaagcggacg gagctgttca ttgccgccga gggcattcac 360

acgggccagt ttgtgtattg cggcaagaag gcccagctca acgttggcaa tgtgctccct 420

gtgggcacca tgcctgaggg tacaatcgtg tgctgcctgg aggagaagcc tggagaccgt 480

ggcaagctgg cccgggcatc agggaactat gccaccgtta tctcccacaa ccctgagacc 540

aagaagaccc gtgtgaagct gccctccggc tccaagaagg ttatctcctc agccaacaga 600

gctgtggttg gtgtggtggc tggaggtggc cgaattgaca aacccatctt gaaggctggc 660

cgggcgtacc acaaatataa ggcaaagagg aactgctggc cacgagtacg gggtgtggcc 720

atgaatcctg tggagcatcc ttttggaggt ggcaaccacc agcacatcgg caagccctcc 780

accatccgca gagatgcccc tgctggccgc aaagtgggtc tcattgctgc ccgccggact 840

ggacgtctcc ggggaaccaa gactgtgcag gagaaagaga actagtgctg agggcctcaa 900

taaagtttgt gtttatgcca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaa 967

<210> 5
<211> 9
<212> PRT
<213> Homo sapiens

<400> 5

Ala Lys Val Val Phe Arg Asp Pro Tyr
1 5

<210> 6
<211> 9
<212> PRT
<213> Homo sapiens

<400> 6

Gly Ile His Thr Gly Gln Phe Val Tyr
1 5

<210> 7
<211> 9

<212> PRT
<213> Homo sapiens

<400> 7

Lys Leu Ala Arg Ala Ser Gly Asn Tyr
1 5

<210> 8
<211> 9
<212> PRT
<213> Homo sapiens

<400> 8

Lys Ala Gly Arg Ala Tyr His Lys Tyr
1 5

<210> 9
<211> 9
<212> PRT
<213> Homo sapiens

<400> 9

Pro Ile Leu Lys Ala Gly Arg Ala Tyr
1 5

<210> 10
<211> 9
<212> PRT
<213> Homo sapiens

<400> 10

Lys Leu Pro Ser Gly Ser Lys Lys Val
1 5

<210> 11
<211> 9
<212> PRT
<213> Homo sapiens

<400> 11

Ser Ala Asn Arg Ala Val Val Gly Val
1 5

<210> 12
<211> 9
<212> PRT
<213> Homo sapiens

<400> 12

Tyr Ile Lys Gly Ile Val Lys Asp Ile
1 5

<210> 13
<211> 9
<212> PRT
<213> Homo sapiens

<400> 13

Leu Asn Ile Gly Asn Val Leu Pro Val
1 5

<210> 14
<211> 9
<212> PRT
<213> Homo sapiens

<400> 14

Gly Arg Gly Ala Pro Leu Ala Lys Val
1 5

<210> 15
<211> 9
<212> PRT
<213> Homo sapiens

<400> 15

Arg Ala Ser Gly Asn Tyr Ala Thr Val
1 5

<210> 16
<211> 9
<212> PRT
<213> Homo sapiens

<400> 16

Val Ile Ser Ser Ala Asn Arg Ala Val
1 5

<210> 17
<211> 9
<212> PRT
<213> Homo sapiens

<400> 17

Arg Ile Asp Lys Pro Ile Leu Lys Ala
1 5

<210> 18

<211> 9
<212> PRT
<213> Homo sapiens

<400> 18

Ile Ala Ala Arg Arg Thr Gly Arg Leu
1 5

<210> 19
<211> 9
<212> PRT
<213> Homo sapiens

<400> 19

Ile Ala Ala Glu Gly Ile His Thr Gly
1 5

<210> 20
<211> 9
<212> PRT
<213> Homo sapiens

<400> 20

Lys Ala Gln Leu Asn Ile Gly Asn Val
1 5

<210> 21
<211> 9
<212> PRT
<213> Homo sapiens

<400> 21

Ala Pro Ala Gly Arg Lys Val Gly Leu
1 5

<210> 22
<211> 9
<212> PRT
<213> Homo sapiens

<400> 22

Lys Gly Ala Ala Arg Leu Arg Ala Val
1 5

<210> 23
<211> 9
<212> PRT
<213> Homo sapiens

<400> 23

Gly Thr Met Pro Glu Gly Thr Ile Val
1 5

<210> 24
<211> 9
<212> PRT
<213> Homo sapiens

<400> 24

Asn Cys Trp Pro Arg Val Arg Gly Val
1 5

<210> 25
<211> 9
<212> PRT
<213> Homo sapiens

<400> 25

Gly Arg Leu Arg Gly Thr Lys Thr Val
1 5

<210> 26
<211> 9
<212> PRT
<213> Homo sapiens

<400> 26

Ile Ile His Asp Pro Gly Arg Gly Ala
1 5

<210> 27
<211> 9
<212> PRT
<213> Homo sapiens

<400> 27

Glu Leu Phe Ile Ala Ala Glu Gly Ile
1 5

<210> 28
<211> 9
<212> PRT
<213> Homo sapiens

<400> 28

Tyr Arg Phe Lys Lys Arg Thr Glu Leu
1 5

<210> 29
<211> 9
<212> PRT
<213> Homo sapiens

<400> 29

Val Tyr Cys Gly Lys Lys Ala Gln Leu
1 5

<210> 30
<211> 9
<212> PRT
<213> Homo sapiens

<400> 30

Ala Asn Arg Ala Val Val Gly Val Val
1 5

<210> 31
<211> 9
<212> PRT
<213> Homo sapiens

<400> 31

Arg Asp Ala Pro Ala Gly Arg Lys Val
1 5

<210> 32
<211> 9
<212> PRT
<213> Homo sapiens

<400> 32

Val Ile Arg Gly Gln Arg Lys Gly Ala
1 5

<210> 33
<211> 9
<212> PRT
<213> Homo sapiens

<400> 33

Gly Gln Arg Lys Gly Ala Gly Ser Val
1 5

<210> 34
<211> 9
<212> PRT
<213> Homo sapiens

<400> 34

Ala Gly Ser Val Phe Arg Ala His Val
1 5

<210> 35
<211> 9
<212> PRT
<213> Homo sapiens

<400> 35

Lys His Arg Lys Gly Ala Ala Arg Leu
1 5

<210> 36
<211> 9
<212> PRT
<213> Homo sapiens

<400> 36

Phe Ile Ala Ala Glu Gly Ile His Thr
1 5

<210> 37
<211> 9
<212> PRT
<213> Homo sapiens

<400> 37

Ala Gln Leu Asn Ile Gly Asn Val Leu
1 5

<210> 38
<211> 9
<212> PRT
<213> Homo sapiens

<400> 38

Gln Leu Asn Ile Gly Asn Val Leu Pro
1 5

<210> 39
<211> 9
<212> PRT
<213> Homo sapiens

<400> 39

Val Leu Pro Val Gly Thr Met Pro Glu
1 5

<210> 40
<211> 9
<212> PRT
<213> Homo sapiens

<400> 40

Ala Val Val Gly Val Val Ala Gly Gly
1 5

<210> 41
<211> 9
<212> PRT
<213> Homo sapiens

<400> 41

Gly Val Val Ala Gly Gly Gly Arg Ile
1 5

<210> 42
<211> 9
<212> PRT
<213> Homo sapiens

<400> 42

Ile Leu Lys Ala Gly Arg Ala Tyr His
1 5

<210> 43
<211> 9
<212> PRT
<213> Homo sapiens

<400> 43

Gln His Ile Gly Lys Pro Ser Thr Ile
1 5

<210> 44
<211> 9
<212> PRT
<213> Homo sapiens

<400> 44

Gly Leu Ile Ala Ala Arg Arg Thr Gly
1 5

<210> 45
<211> 9
<212> PRT
<213> Homo sapiens

<400> 45

Arg Val Lys Leu Pro Ser Gly Ser Lys
1 5

<210> 46
<211> 9
<212> PRT
<213> Homo sapiens

<400> 46

Ile Leu Lys Ala Gly Arg Ala Tyr His
1 5

<210> 47
<211> 9
<212> PRT
<213> Homo sapiens

<400> 47

Lys Leu Ala Arg Ala Ser Gly Asn Tyr
1 5

<210> 48
<211> 9
<212> PRT
<213> Homo sapiens

<400> 48

Arg Val Arg Gly Val Ala Met Asn Pro
1 5

<210> 49
<211> 9
<212> PRT
<213> Homo sapiens

<400> 49

Lys Val Gly Leu Ile Ala Ala Arg Arg
1 5

<210> 50
<211> 9
<212> PRT
<213> Homo sapiens

<400> 50

Arg Leu Arg Gly Thr Lys Thr Val Gln
1 5

<210> 51
<211> 9
<212> PRT
<213> Homo sapiens

<400> 51

His Gly Tyr Ile Lys Gly Ile Val Lys
1 5

<210> 52
<211> 9
<212> PRT
<213> Homo sapiens

<400> 52

Val Ile Ser His Asn Pro Glu Thr Lys
1 5

<210> 53
<211> 9
<212> PRT
<213> Homo sapiens

<400> 53

Arg Thr Gly Arg Leu Arg Gly Thr Lys
1 5

<210> 54
<211> 9
<212> PRT
<213> Homo sapiens

<400> 54

Arg Val Ile Arg Gly Gln Arg Lys Gly
1 5

<210> 55
<211> 9
<212> PRT
<213> Homo sapiens

<400> 55

Ser Val Phe Arg Ala His Val Lys His
1 5

<210> 56
<211> 9
<212> PRT

<213> Homo sapiens

<400> 56

Arg Leu Arg Ala Val Asp Phe Ala Glu
1 5

<210> 57
<211> 9
<212> PRT
<213> Homo sapiens

<400> 57

Asn Val Leu Pro Val Gly Thr Met Pro
1 5

<210> 58
<211> 9
<212> PRT
<213> Homo sapiens

<400> 58

Val Lys Leu Pro Ser Gly Ser Lys Lys
1 5

<210> 59
<211> 9
<212> PRT
<213> Homo sapiens

<400> 59

Ala Ala Arg Leu Arg Ala Val Asp Phe
1 5

<210> 60
<211> 9
<212> PRT
<213> Homo sapiens

<400> 60

Pro Gly Arg Gly Ala Pro Leu Ala Lys
1 5

<210> 61
<211> 9
<212> PRT
<213> Homo sapiens

<400> 61

Gly Ile His Thr Gly Gln Phe Val Tyr

1 5

<210> 62
<211> 9
<212> PRT
<213> Homo sapiens

<400> 62

Pro Ile Leu Lys Ala Gly Arg Ala Tyr
1 5

<210> 63
<211> 9
<212> PRT
<213> Homo sapiens

<400> 63

Arg Ala Tyr His Lys Tyr Lys Ala Lys
1 5

<210> 64
<211> 9
<212> PRT
<213> Homo sapiens

<400> 64

Gly Val Ala Met Asn Pro Val Glu His
1 5

<210> 65
<211> 9
<212> PRT
<213> Homo sapiens

<400> 65

Arg Arg Asp Ala Pro Ala Gly Arg Lys
1 5

<210> 66
<211> 9
<212> PRT
<213> Homo sapiens

<400> 66

Gly Leu Ile Ala Ala Arg Arg Thr Gly
1 5

<210> 67
<211> 9

<212> PRT
<213> Homo sapiens

<400> 67

Gln Arg Lys Gly Ala Gly Ser Val Phe
1 5

<210> 68
<211> 9
<212> PRT
<213> Homo sapiens

<400> 68

Gly Ser Val Phe Arg Ala His Val Lys
1 5

<210> 69
<211> 9
<212> PRT
<213> Homo sapiens

<400> 69

Lys Val Val Phe Arg Asp Pro Tyr Arg
1 5

<210> 70
<211> 9
<212> PRT
<213> Homo sapiens

<400> 70

Gln Leu Asn Ile Gly Asn Val Leu Pro
1 5

<210> 71
<211> 9
<212> PRT
<213> Homo sapiens

<400> 71

Lys Val Ile Ser Ser Ala Asn Arg Ala
1 5

<210> 72
<211> 9
<212> PRT
<213> Homo sapiens

<400> 72

Ala Val Val Gly Val Val Ala Gly Gly
1 5

<210> 73
<211> 9
<212> PRT
<213> Homo sapiens

<400> 73

Leu Ile Ala Ala Arg Arg Thr Gly Arg
1 5

<210> 74
<211> 9
<212> PRT
<213> Homo sapiens

<400> 74

Val Val Phe Arg Asp Pro Tyr Arg Phe
1 5

<210> 75
<211> 9
<212> PRT
<213> Homo sapiens

<400> 75

Thr Ile Val Cys Cys Leu Glu Glu Lys
1 5

<210> 76
<211> 9
<212> PRT
<213> Homo sapiens

<400> 76

Cys Leu Glu Glu Lys Pro Gly Asp Arg
1 5

<210> 77
<211> 9
<212> PRT
<213> Homo sapiens

<400> 77

Gly Val Val Ala Gly Gly Gly Arg Ile
1 5

<210> 78

<211> 9
<212> PRT
<213> Homo sapiens

<400> 78

Val Val Ala Gly Gly Gly Arg Ile Asp
1 5

<210> 79
<211> 9
<212> PRT
<213> Homo sapiens

<400> 79

Leu Lys Ala Gly Arg Ala Tyr His Lys
1 5

<210> 80
<211> 9
<212> PRT
<213> Homo sapiens

<400> 80

Ala Gly Arg Ala Tyr His Lys Tyr Lys
1 5

<210> 81
<211> 9
<212> PRT
<213> Homo sapiens

<400> 81

Thr Ile Arg Arg Asp Ala Pro Ala Gly
1 5

<210> 82
<211> 9
<212> PRT
<213> Homo sapiens

<400> 82

Phe Val Tyr Cys Gly Lys Lys Ala Gln
1 5

<210> 83
<211> 9
<212> PRT
<213> Homo sapiens

<400> 83

Gly Arg Val Ile Arg Gly Gln Arg Lys
1 5

<210> 84
<211> 9
<212> PRT
<213> Homo sapiens

<400> 84

Arg Lys Gly Ala Gly Ser Val Phe Arg
1 5

<210> 85
<211> 9
<212> PRT
<213> Homo sapiens

<400> 85

Phe Ala Glu Arg His Gly Tyr Ile Lys
1 5

<210> 86
<211> 9
<212> PRT
<213> Homo sapiens

<400> 86

Ala Pro Leu Ala Lys Val Val Phe Arg
1 5

<210> 87
<211> 9
<212> PRT
<213> Homo sapiens

<400> 87

Glu Glu Lys Pro Gly Asp Arg Gly Lys
1 5

<210> 88
<211> 9
<212> PRT
<213> Homo sapiens

<400> 88

Ser Ser Ala Asn Arg Ala Val Val Gly
1 5

<210> 89
<211> 9
<212> PRT
<213> Homo sapiens

<400> 89

Gly Arg Ile Asp Lys Pro Ile Leu Lys
1 5

<210> 90
<211> 9
<212> PRT
<213> Homo sapiens

<400> 90

Gln His Ile Gly Lys Pro Ser Thr Ile
1 5

<210> 91
<211> 9
<212> PRT
<213> Homo sapiens

<400> 91

Ala Ala Arg Arg Thr Gly Arg Leu Arg
1 5

<210> 92
<211> 9
<212> PRT
<213> Homo sapiens

<400> 92

His Val Lys His Arg Lys Gly Ala Ala
1 5

<210> 93
<211> 9
<212> PRT
<213> Homo sapiens

<400> 93

Val Lys His Arg Lys Gly Ala Ala Arg
1 5

<210> 94
<211> 9
<212> PRT
<213> Homo sapiens

<400> 94

Arg Gly Ala Pro Leu Ala Lys Val Val
1 5

<210> 95
<211> 9
<212> PRT
<213> Homo sapiens

<400> 95

Pro Glu Thr Lys Lys Thr Arg Val Lys
1 5

<210> 96
<211> 9
<212> PRT
<213> Homo sapiens

<400> 96

Lys Leu Pro Ser Gly Ser Lys Lys Val
1 5

<210> 97
<211> 9
<212> PRT
<213> Homo sapiens

<400> 97

Val Val Gly Val Val Ala Gly Gly Gly
1 5

<210> 98
<211> 9
<212> PRT
<213> Homo sapiens

<400> 98

Val Ala Gly Gly Gly Arg Ile Asp Lys
1 5

<210> 99
<211> 9
<212> PRT
<213> Homo sapiens

<400> 99

Arg Ile Asp Lys Pro Ile Leu Lys Ala
1 5

<210> 100
<211> 9
<212> PRT
<213> Homo sapiens

<400> 100

Val Tyr Cys Gly Lys Lys Ala Gln Leu
1 5

<210> 101
<211> 9
<212> PRT
<213> Homo sapiens

<400> 101

Asp Phe Ala Glu Arg His Gly Tyr Ile
1 5

<210> 102
<211> 9
<212> PRT
<213> Homo sapiens

<400> 102

Arg Phe Lys Lys Arg Thr Glu Leu Phe
1 5

<210> 103
<211> 9
<212> PRT
<213> Homo sapiens

<400> 103

Gly Tyr Ile Lys Gly Ile Val Lys Asp
1 5

<210> 104
<211> 9
<212> PRT
<213> Homo sapiens

<400> 104

Ala Pro Ala Gly Arg Lys Val Gly Leu
1 5

<210> 105
<211> 9
<212> PRT
<213> Homo sapiens

<400> 105

Trp Pro Arg Val Arg Gly Val Ala Met
1 5

<210> 106
<211> 9
<212> PRT
<213> Homo sapiens

<400> 106

Leu Pro Ser Gly Ser Lys Lys Val Ile
1 5

<210> 107
<211> 9
<212> PRT
<213> Homo sapiens

<400> 107

Lys Pro Ser Thr Ile Arg Arg Asp Ala
1 5

<210> 108
<211> 9
<212> PRT
<213> Homo sapiens

<400> 108

Lys Pro Gly Asp Arg Gly Lys Leu Ala
1 5

<210> 109
<211> 9
<212> PRT
<213> Homo sapiens

<400> 109

Asp Pro Gly Arg Gly Ala Pro Leu Ala
1 5

<210> 110
<211> 9
<212> PRT
<213> Homo sapiens

<400> 110

Ala Pro Leu Ala Lys Val Val Phe Arg
1 5

<210> 111
<211> 9
<212> PRT
<213> Homo sapiens

<400> 111

Asn Pro Glu Thr Lys Lys Thr Arg Val
1 5

<210> 112
<211> 9
<212> PRT
<213> Homo sapiens

<400> 112

Lys Pro Ile Leu Lys Ala Gly Arg Ala
1 5

<210> 113
<211> 9
<212> PRT
<213> Homo sapiens

<400> 113

Asp Pro Tyr Arg Phe Lys Lys Arg Thr
1 5

<210> 114
<211> 9
<212> PRT
<213> Homo sapiens

<400> 114

Lys His Arg Lys Gly Ala Ala Arg Leu
1 5

<210> 115
<211> 9
<212> PRT
<213> Homo sapiens

<400> 115

His Asp Pro Gly Arg Gly Ala Pro Leu
1 5

<210> 116
<211> 9
<212> PRT

<213> Homo sapiens

<400> 116

Glu Thr Lys Lys Thr Arg Val Lys Leu
1 5

<210> 117
<211> 9
<212> PRT
<213> Homo sapiens

<400> 117

Ala Glu Gly Ile His Thr Gly Gln Phe
1 5

<210> 118
<211> 9
<212> PRT
<213> Homo sapiens

<400> 118

Pro Glu Gly Thr Ile Val Cys Cys Leu
1 5

<210> 119
<211> 9
<212> PRT
<213> Homo sapiens

<400> 119

Ala Gln Leu Asn Ile Gly Asn Val Leu
1 5

<210> 120
<211> 9
<212> PRT
<213> Homo sapiens

<400> 120

Ala Ala Arg Leu Arg Ala Val Asp Phe
1 5

<210> 121
<211> 9
<212> PRT
<213> Homo sapiens

<400> 121

Ala Met Asn Pro Val Glu His Pro Phe

1 5

<210> 122
<211> 9
<212> PRT
<213> Homo sapiens

<400> 122

Glu Arg His Gly Tyr Ile Lys Gly Ile
1 5

<210> 123
<211> 9
<212> PRT
<213> Homo sapiens

<400> 123

Glu Glu Lys Pro Gly Asp Arg Gly Lys
1 5

<210> 124
<211> 9
<212> PRT
<213> Homo sapiens

<400> 124

Glu Lys Pro Gly Asp Arg Gly Lys Leu
1 5

<210> 125
<211> 9
<212> PRT
<213> Homo sapiens

<400> 125

Ala Pro Ala Gly Arg Lys Val Gly Leu
1 5

<210> 126
<211> 9
<212> PRT
<213> Homo sapiens

<400> 126

Ala Glu Arg His Gly Tyr Ile Lys Gly
1 5

<210> 127
<211> 9

<212> PRT
<213> Homo sapiens

<400> 127

Glu Thr Lys Lys Thr Arg Val Lys Leu
1 5

<210> 128
<211> 9
<212> PRT
<213> Homo sapiens

<400> 128

Leu Pro Ser Gly Ser Lys Lys Val Ile
1 5

<210> 129
<211> 9
<212> PRT
<213> Homo sapiens

<400> 129

Asn Pro Glu Thr Lys Lys Thr Arg Val
1 5

<210> 130
<211> 9
<212> PRT
<213> Homo sapiens

<400> 130

Pro Ala Gly Arg Lys Val Gly Leu Ile
1 5

<210> 131
<211> 9
<212> PRT
<213> Homo sapiens

<400> 131

Arg Ala Ser Gly Asn Tyr Ala Thr Val
1 5

<210> 132
<211> 9
<212> PRT
<213> Homo sapiens

<400> 132

Ser Ala Asn Arg Ala Val Val Gly Val
1 5

<210> 133
<211> 9
<212> PRT
<213> Homo sapiens

<400> 133

Asp Pro Tyr Arg Phe Lys Lys Arg Thr
1 5

<210> 134
<211> 9
<212> PRT
<213> Homo sapiens

<400> 134

Asp Ala Pro Ala Gly Arg Lys Val Gly
1 5

<210> 135
<211> 9
<212> PRT
<213> Homo sapiens

<400> 135

Arg Gly Ala Pro Leu Ala Lys Val Val
1 5

<210> 136
<211> 9
<212> PRT
<213> Homo sapiens

<400> 136

Lys Ala Gln Leu Asn Ile Gly Asn Val
1 5

<210> 137
<211> 9
<212> PRT
<213> Homo sapiens

<400> 137

Val Gly Thr Met Pro Glu Gly Thr Ile
1 5

<210> 138

<211> 9
<212> PRT
<213> Homo sapiens

<400> 138

Phe Gly Gly Gly Asn His Gln His Ile
1 5

<210> 139
<211> 9
<212> PRT
<213> Homo sapiens

<400> 139

Ile Ala Ala Arg Arg Thr Gly Arg Leu
1 5

<210> 140
<211> 9
<212> PRT
<213> Homo sapiens

<400> 140

Cys Gly Lys Lys Ala Gln Leu Asn Ile
1 5

<210> 141
<211> 9
<212> PRT
<213> Homo sapiens

<400> 141

Ala Pro Ala Gly Arg Lys Val Gly Leu
1 5

<210> 142
<211> 9
<212> PRT
<213> Homo sapiens

<400> 142

Lys Gly Ala Ala Arg Leu Arg Ala Val
1 5

<210> 143
<211> 9
<212> PRT
<213> Homo sapiens

<400> 143

Ala Pro Leu Ala Lys Val Val Phe Arg
1 5

<210> 144
<211> 9
<212> PRT
<213> Homo sapiens

<400> 144

Ile Ala Ala Glu Gly Ile His Thr Gly
1 5

<210> 145
<211> 9
<212> PRT
<213> Homo sapiens

<400> 145

Gly Gly Gly Arg Ile Asp Lys Pro Ile
1 5

<210> 146
<211> 9
<212> PRT
<213> Homo sapiens

<400> 146

Asp Phe Ala Glu Arg His Gly Tyr Ile
1 5

<210> 147
<211> 9
<212> PRT
<213> Homo sapiens

<400> 147

Tyr Ile Lys Gly Ile Val Lys Asp Ile
1 5

<210> 148
<211> 9
<212> PRT
<213> Homo sapiens

<400> 148

Leu Ala Lys Val Val Phe Arg Asp Pro
1 5

<210> 149
<211> 9
<212> PRT
<213> Homo sapiens

<400> 149

Ala Ser Gly Asn Tyr Ala Thr Val Ile
1 5

<210> 150
<211> 9
<212> PRT
<213> Homo sapiens

<400> 150

Ala Asn Arg Ala Val Val Gly Val Val
1 5

<210> 151
<211> 9
<212> PRT
<213> Homo sapiens

<400> 151

Arg Ala Tyr His Lys Tyr Lys Ala Lys
1 5

<210> 152
<211> 9
<212> PRT
<213> Homo sapiens

<400> 152

Ala Gly Ser Val Phe Arg Ala His Val
1 5

<210> 153
<211> 9
<212> PRT
<213> Homo sapiens

<400> 153

His Gly Tyr Ile Lys Gly Ile Val Lys
1 5

<210> 154
<211> 9
<212> PRT
<213> Homo sapiens

<400> 154

Asp Pro Gly Arg Gly Ala Pro Leu Ala
1 5

<210> 155
<211> 9
<212> PRT
<213> Homo sapiens

<400> 155

Gly Ala Pro Leu Ala Lys Val Val Phe
1 5

<210> 156
<211> 9
<212> PRT
<213> Homo sapiens

<400> 156

Glu Gly Ile His Thr Gly Gln Phe Val
1 5

<210> 157
<211> 9
<212> PRT
<213> Homo sapiens

<400> 157

Met Pro Glu Gly Thr Ile Val Cys Cys
1 5

<210> 158
<211> 9
<212> PRT
<213> Homo sapiens

<400> 158

Leu Ala Arg Ala Ser Gly Asn Tyr Ala
1 5

<210> 159
<211> 9
<212> PRT
<213> Homo sapiens

<400> 159

Gln His Ile Gly Lys Pro Ser Thr Ile
1 5

<210> 160
<211> 15
<212> PRT
<213> Homo sapiens

<400> 160

Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val
1 5 10 15

<210> 161
<211> 15
<212> PRT
<213> Homo sapiens

<400> 161

Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys
1 5 10 15

<210> 162
<211> 15
<212> PRT
<213> Homo sapiens

<400> 162

Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala
1 5 10 15

<210> 163
<211> 15
<212> PRT
<213> Homo sapiens

<400> 163

Arg Ile Asp Lys Pro Ile Leu Lys Ala Gly Arg Ala Tyr His Lys
1 5 10 15

<210> 164
<211> 15
<212> PRT
<213> Homo sapiens

<400> 164

Gly Ala Pro Leu Ala Lys Val Val Phe Arg Asp Pro Tyr Arg Phe
1 5 10 15

<210> 165
<211> 15
<212> PRT
<213> Homo sapiens

<400> 165

Lys Arg Thr Glu Leu Phe Ile Ala Ala Glu Gly Ile His Thr Gly
1 5 10 15

<210> 166
<211> 15
<212> PRT
<213> Homo sapiens

<400> 166

Asn Arg Ala Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp
1 5 10 15

<210> 167
<211> 15
<212> PRT
<213> Homo sapiens

<400> 167

Arg Lys Gly Ala Ala Arg Leu Arg Ala Val Asp Phe Ala Glu Arg
1 5 10 15

<210> 168
<211> 15
<212> PRT
<213> Homo sapiens

<400> 168

Leu Ala Lys Val Val Phe Arg Asp Pro Tyr Arg Phe Lys Lys Arg
1 5 10 15

<210> 169
<211> 15
<212> PRT
<213> Homo sapiens

<400> 169

Arg Gly Lys Leu Ala Arg Ala Ser Gly Asn Tyr Ala Thr Val Ile
1 5 10 15

<210> 170
<211> 15
<212> PRT
<213> Homo sapiens

<400> 170

Ser Ser Ala Asn Arg Ala Val Val Gly Val Val Ala Gly Gly Gly
1 5 10 15

<210> 171
<211> 15
<212> PRT
<213> Homo sapiens

<400> 171

Arg Ala Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp Lys
1 5 10 15

<210> 172
<211> 15
<212> PRT
<213> Homo sapiens

<400> 172

Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val Glu His Pro
1 5 10 15

<210> 173
<211> 15
<212> PRT
<213> Homo sapiens

<400> 173

Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu
1 5 10 15

<210> 174
<211> 15
<212> PRT
<213> Homo sapiens

<400> 174

His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro
1 5 10 15

<210> 175
<211> 15
<212> PRT
<213> Homo sapiens

<400> 175

Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala
1 5 10 15

<210> 176
<211> 15
<212> PRT

<213> Homo sapiens

<400> 176

Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu
1 5 10 15

<210> 177
<211> 15
<212> PRT
<213> Homo sapiens

<400> 177

Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile Val Cys Cys
1 5 10 15

<210> 178
<211> 15
<212> PRT
<213> Homo sapiens

<400> 178

Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr
1 5 10 15

<210> 179
<211> 15
<212> PRT
<213> Homo sapiens

<400> 179

Arg His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp
1 5 10 15

<210> 180
<211> 15
<212> PRT
<213> Homo sapiens

<400> 180

Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala Ala Glu
1 5 10 15

<210> 181
<211> 15
<212> PRT
<213> Homo sapiens

<400> 181

Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile

1 5 10 15

<210> 182
<211> 15
<212> PRT
<213> Homo sapiens

<400> 182

Gly Arg Ala Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Pro
1 5 10 15

<210> 183
<211> 15
<212> PRT
<213> Homo sapiens

<400> 183

Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe Arg Ala His
1 5 10 15

<210> 184
<211> 15
<212> PRT
<213> Homo sapiens

<400> 184

Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe Val Tyr Cys
1 5 10 15

<210> 185
<211> 15
<212> PRT
<213> Homo sapiens

<400> 185

Lys Ala Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met
1 5 10 15

<210> 186
<211> 15
<212> PRT
<213> Homo sapiens

<400> 186

Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile Val Cys Cys Leu
1 5 10 15

<210> 187
<211> 15

<212> PRT
<213> Homo sapiens

<400> 187

Gly Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly
1 5 10 15

<210> 188
<211> 15
<212> PRT
<213> Homo sapiens

<400> 188

Met Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val
1 5 10 15

<210> 189
<211> 15
<212> PRT
<213> Homo sapiens

<400> 189

Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly
1 5 10 15

<210> 190
<211> 15
<212> PRT
<213> Homo sapiens

<400> 190

Thr Glu Leu Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe
1 5 10 15

<210> 191
<211> 15
<212> PRT
<213> Homo sapiens

<400> 191

Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe Val Tyr Cys Gly
1 5 10 15

<210> 192
<211> 15
<212> PRT
<213> Homo sapiens

<400> 192

Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr
1 5 10 15

<210> 193
<211> 15
<212> PRT
<213> Homo sapiens

<400> 193

Lys Pro Gly Asp Arg Gly Lys Leu Ala Arg Ala Ser Gly Asn Tyr
1 5 10 15

<210> 194
<211> 15
<212> PRT
<213> Homo sapiens

<400> 194

Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser
1 5 10 15

<210> 195
<211> 15
<212> PRT
<213> Homo sapiens

<400> 195

Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp Lys Pro Ile
1 5 10 15

<210> 196
<211> 15
<212> PRT
<213> Homo sapiens

<400> 196

Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Pro Arg Val Arg
1 5 10 15

<210> 197
<211> 15
<212> PRT
<213> Homo sapiens

<400> 197

Ala Pro Ala Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr
1 5 10 15

<210> 198

<211> 15
<212> PRT
<213> Homo sapiens

<400> 198

Arg Arg Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys
1 5 10 15

<210> 199
<211> 15
<212> PRT
<213> Homo sapiens

<400> 199

Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe Arg
1 5 10 15

<210> 200
<211> 15
<212> PRT
<213> Homo sapiens

<400> 200

Ala Val Asp Phe Ala Glu Arg His Gly Tyr Ile Lys Gly Ile Val
1 5 10 15

<210> 201
<211> 15
<212> PRT
<213> Homo sapiens

<400> 201

His Thr Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn
1 5 10 15

<210> 202
<211> 15
<212> PRT
<213> Homo sapiens

<400> 202

Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn Ile Gly Asn
1 5 10 15

<210> 203
<211> 15
<212> PRT
<213> Homo sapiens

<400> 203

Glu Gly Thr Ile Val Cys Cys Leu Glu Glu Lys Pro Gly Asp Arg
1 5 10 15

<210> 204
<211> 15
<212> PRT
<213> Homo sapiens

<400> 204

Gly Thr Ile Val Cys Cys Leu Glu Glu Lys Pro Gly Asp Arg Gly
1 5 10 15

<210> 205
<211> 15
<212> PRT
<213> Homo sapiens

<400> 205

Thr Lys Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val
1 5 10 15

<210> 206
<211> 15
<212> PRT
<213> Homo sapiens

<400> 206

Ala Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp Lys Pro
1 5 10 15

<210> 207
<211> 15
<212> PRT
<213> Homo sapiens

<400> 207

Met Asn Pro Val Glu His Pro Phe Gly Gly Gly Asn His Gln His
1 5 10 15

<210> 208
<211> 15
<212> PRT
<213> Homo sapiens

<400> 208

Glu His Pro Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro
1 5 10 15

<210> 209
<211> 15
<212> PRT
<213> Homo sapiens

<400> 209

Pro Ser Thr Ile Arg Arg Asp Ala Pro Ala Gly Arg Lys Val Gly
1 5 10 15

<210> 210
<211> 15
<212> PRT
<213> Homo sapiens

<400> 210

Thr Ile Arg Arg Asp Ala Pro Ala Gly Arg Lys Val Gly Leu Ile
1 5 10 15

<210> 211
<211> 15
<212> PRT
<213> Homo sapiens

<400> 211

Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu
1 5 10 15

<210> 212
<211> 15
<212> PRT
<213> Homo sapiens

<400> 212

Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe Arg Ala
1 5 10 15

<210> 213
<211> 15
<212> PRT
<213> Homo sapiens

<400> 213

Arg Ala His Val Lys His Arg Lys Gly Ala Ala Arg Leu Arg Ala
1 5 10 15

<210> 214
<211> 15
<212> PRT
<213> Homo sapiens

<400> 214

Ala His Val Lys His Arg Lys Gly Ala Ala Arg Leu Arg Ala Val
1 5 10 15

<210> 215
<211> 15
<212> PRT
<213> Homo sapiens

<400> 215

Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys
1 5 10 15

<210> 216
<211> 15
<212> PRT
<213> Homo sapiens

<400> 216

Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys Val Val
1 5 10 15

<210> 217
<211> 15
<212> PRT
<213> Homo sapiens

<400> 217

Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys Val Val Phe Arg Asp
1 5 10 15

<210> 218
<211> 15
<212> PRT
<213> Homo sapiens

<400> 218

Gly Lys Lys Ala Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly
1 5 10 15

<210> 219
<211> 15
<212> PRT
<213> Homo sapiens

<400> 219

Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly
1 5 10 15

<210> 220
<211> 15
<212> PRT
<213> Homo sapiens

<400> 220

Leu Glu Glu Lys Pro Gly Asp Arg Gly Lys Leu Ala Arg Ala Ser
1 5 10 15

<210> 221
<211> 15
<212> PRT
<213> Homo sapiens

<400> 221

Leu Ala Arg Ala Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn
1 5 10 15

<210> 222
<211> 15
<212> PRT
<213> Homo sapiens

<400> 222

Lys Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile
1 5 10 15

<210> 223
<211> 15
<212> PRT
<213> Homo sapiens

<400> 223

Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser
1 5 10 15

<210> 224
<211> 15
<212> PRT
<213> Homo sapiens

<400> 224

Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala
1 5 10 15

<210> 225
<211> 15
<212> PRT
<213> Homo sapiens

<400> 225

Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val
1 5 10 15

<210> 226
<211> 15
<212> PRT
<213> Homo sapiens

<400> 226

Lys Pro Ile Leu Lys Ala Gly Arg Ala Tyr His Lys Tyr Lys Ala
1 5 10 15

<210> 227
<211> 15
<212> PRT
<213> Homo sapiens

<400> 227

Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val Glu His
1 5 10 15

<210> 228
<211> 15
<212> PRT
<213> Homo sapiens

<400> 228

Val Arg Gly Val Ala Met Asn Pro Val Glu His Pro Phe Gly Gly
1 5 10 15

<210> 229
<211> 15
<212> PRT
<213> Homo sapiens

<400> 229

Gly Gly Gly Asn His Gln His Ile Gly Lys Pro Ser Thr Ile Arg
1 5 10 15

<210> 230
<211> 15
<212> PRT
<213> Homo sapiens

<400> 230

Gly Asn His Gln His Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp
1 5 10 15

<210> 231
<211> 15
<212> PRT
<213> Homo sapiens

<400> 231

Ala Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg
1 5 10 15

<210> 232
<211> 15
<212> PRT
<213> Homo sapiens

<400> 232

Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe
1 5 10 15

<210> 233
<211> 15
<212> PRT
<213> Homo sapiens

<400> 233

Ala Ala Arg Leu Arg Ala Val Asp Phe Ala Glu Arg His Gly Tyr
1 5 10 15

<210> 234
<211> 15
<212> PRT
<213> Homo sapiens

<400> 234

Asp Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys Val
1 5 10 15

<210> 235
<211> 15
<212> PRT
<213> Homo sapiens

<400> 235

Pro Gly Arg Gly Ala Pro Leu Ala Lys Val Val Phe Arg Asp Pro
1 5 10 15

<210> 236
<211> 15
<212> PRT

<213> Homo sapiens

<400> 236

Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala Ala
1 5 10 15

<210> 237
<211> 15
<212> PRT
<213> Homo sapiens

<400> 237

Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn Ile Gly
1 5 10 15

<210> 238
<211> 15
<212> PRT
<213> Homo sapiens

<400> 238

Cys Gly Lys Lys Ala Gln Leu Asn Ile Gly Asn Val Leu Pro Val
1 5 10 15

<210> 239
<211> 15
<212> PRT
<213> Homo sapiens

<400> 239

Val Cys Cys Leu Glu Glu Lys Pro Gly Asp Arg Gly Lys Leu Ala
1 5 10 15

<210> 240
<211> 15
<212> PRT
<213> Homo sapiens

<400> 240

Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val Val
1 5 10 15

<210> 241
<211> 15
<212> PRT
<213> Homo sapiens

<400> 241

Gly Val Ala Met Asn Pro Val Glu His Pro Phe Gly Gly Gly Asn

1 5 10 15

<210> 242
<211> 15
<212> PRT
<213> Homo sapiens

<400> 242

Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro Ser Thr Ile
1 5 10 15

<210> 243
<211> 15
<212> PRT
<213> Homo sapiens

<400> 243

His Gln His Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp Ala Pro
1 5 10 15

<210> 244
<211> 15
<212> PRT
<213> Homo sapiens

<400> 244

Asp Ala Pro Ala Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg
1 5 10 15

<210> 245
<211> 15
<212> PRT
<213> Homo sapiens

<400> 245

Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys Glu Asn
1 5 10 15

<210> 246
<211> 15
<212> PRT
<213> Homo sapiens

<400> 246

Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala
1 5 10 15

<210> 247
<211> 15

<212> PRT
<213> Homo sapiens

<400> 247

Lys Lys Ala Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr
1 5 10 15

<210> 248
<211> 15
<212> PRT
<213> Homo sapiens

<400> 248

Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val
1 5 10 15

<210> 249
<211> 15
<212> PRT
<213> Homo sapiens

<400> 249

Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val Val
1 5 10 15

<210> 250
<211> 15
<212> PRT
<213> Homo sapiens

<400> 250

Lys Val Val Phe Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu
1 5 10 15

<210> 251
<211> 15
<212> PRT
<213> Homo sapiens

<400> 251

Thr Glu Leu Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe
1 5 10 15

<210> 252
<211> 15
<212> PRT
<213> Homo sapiens

<400> 252

Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys
1 5 10 15

<210> 253
<211> 15
<212> PRT
<213> Homo sapiens

<400> 253

Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val
1 5 10 15

<210> 254
<211> 15
<212> PRT
<213> Homo sapiens

<400> 254

Glu His Pro Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro
1 5 10 15

<210> 255
<211> 15
<212> PRT
<213> Homo sapiens

<400> 255

Met Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val
1 5 10 15

<210> 256
<211> 15
<212> PRT
<213> Homo sapiens

<400> 256

Leu Arg Ala Val Asp Phe Ala Glu Arg His Gly Tyr Ile Lys Gly
1 5 10 15

<210> 257
<211> 15
<212> PRT
<213> Homo sapiens

<400> 257

His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro
1 5 10 15

<210> 258

<211> 15
<212> PRT
<213> Homo sapiens

<400> 258

Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala
1 5 10 15

<210> 259
<211> 15
<212> PRT
<213> Homo sapiens

<400> 259

Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala
1 5 10 15

<210> 260
<211> 15
<212> PRT
<213> Homo sapiens

<400> 260

Ala Lys Val Val Phe Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr
1 5 10 15

<210> 261
<211> 15
<212> PRT
<213> Homo sapiens

<400> 261

Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu
1 5 10 15

<210> 262
<211> 15
<212> PRT
<213> Homo sapiens

<400> 262

Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile
1 5 10 15

<210> 263
<211> 15
<212> PRT
<213> Homo sapiens

<400> 263

Arg Gly Lys Leu Ala Arg Ala Ser Gly Asn Tyr Ala Thr Val Ile
1 5 10 15

<210> 264
<211> 15
<212> PRT
<213> Homo sapiens

<400> 264

Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val
1 5 10 15

<210> 265
<211> 15
<212> PRT
<213> Homo sapiens

<400> 265

Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp Lys Pro Ile Leu
1 5 10 15

<210> 266
<211> 15
<212> PRT
<213> Homo sapiens

<400> 266

Asp Lys Pro Ile Leu Lys Ala Gly Arg Ala Tyr His Lys Tyr Lys
1 5 10 15

<210> 267
<211> 15
<212> PRT
<213> Homo sapiens

<400> 267

Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val Glu His Pro
1 5 10 15

<210> 268
<211> 15
<212> PRT
<213> Homo sapiens

<400> 268

Gly Val Ala Met Asn Pro Val Glu His Pro Phe Gly Gly Gly Asn
1 5 10 15

<210> 269
<211> 15
<212> PRT
<213> Homo sapiens

<400> 269

Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu
1 5 10 15

<210> 270
<211> 15
<212> PRT
<213> Homo sapiens

<400> 270

Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly
1 5 10 15

<210> 271
<211> 15
<212> PRT
<213> Homo sapiens

<400> 271

Arg Lys Gly Ala Gly Ser Val Phe Arg Ala His Val Lys His Arg
1 5 10 15

<210> 272
<211> 15
<212> PRT
<213> Homo sapiens

<400> 272

Val Lys His Arg Lys Gly Ala Ala Arg Leu Arg Ala Val Asp Phe
1 5 10 15

<210> 273
<211> 15
<212> PRT
<213> Homo sapiens

<400> 273

Arg Ala Val Asp Phe Ala Glu Arg His Gly Tyr Ile Lys Gly Ile
1 5 10 15

<210> 274
<211> 15
<212> PRT
<213> Homo sapiens

<400> 274

Lys Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile
1 5 10 15

<210> 275
<211> 15
<212> PRT
<213> Homo sapiens

<400> 275

Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val
1 5 10 15

<210> 276
<211> 15
<212> PRT
<213> Homo sapiens

<400> 276

Ile Leu Lys Ala Gly Arg Ala Tyr His Lys Tyr Lys Ala Lys Arg
1 5 10 15

<210> 277
<211> 15
<212> PRT
<213> Homo sapiens

<400> 277

Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala
1 5 10 15

<210> 278
<211> 15
<212> PRT
<213> Homo sapiens

<400> 278

Gly Ser Val Phe Arg Ala His Val Lys His Arg Lys Gly Ala Ala
1 5 10 15

<210> 279
<211> 15
<212> PRT
<213> Homo sapiens

<400> 279

Arg His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp
1 5 10 15

<210> 280
<211> 15
<212> PRT
<213> Homo sapiens

<400> 280

Thr Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn Ile
1 5 10 15

<210> 281
<211> 15
<212> PRT
<213> Homo sapiens

<400> 281

Gly Arg Ala Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Pro
1 5 10 15

<210> 282
<211> 15
<212> PRT
<213> Homo sapiens

<400> 282

Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr
1 5 10 15

<210> 283
<211> 15
<212> PRT
<213> Homo sapiens

<400> 283

Ser Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val
1 5 10 15

<210> 284
<211> 15
<212> PRT
<213> Homo sapiens

<400> 284

Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala Ala Glu
1 5 10 15

<210> 285
<211> 15
<212> PRT
<213> Homo sapiens

<400> 285

Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr
1 5 10 15

<210> 286
<211> 15
<212> PRT
<213> Homo sapiens

<400> 286

Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys Glu Asn
1 5 10 15

<210> 287
<211> 15
<212> PRT
<213> Homo sapiens

<400> 287

His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro
1 5 10 15

<210> 288
<211> 15
<212> PRT
<213> Homo sapiens

<400> 288

Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile Val Cys Cys
1 5 10 15

<210> 289
<211> 15
<212> PRT
<213> Homo sapiens

<400> 289

Thr Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser
1 5 10 15

<210> 290
<211> 15
<212> PRT
<213> Homo sapiens

<400> 290

Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val Val
1 5 10 15

<210> 291
<211> 15
<212> PRT
<213> Homo sapiens

<400> 291

Leu Arg Ala Val Asp Phe Ala Glu Arg His Gly Tyr Ile Lys Gly
1 5 10 15

<210> 292
<211> 15
<212> PRT
<213> Homo sapiens

<400> 292

Arg Thr Glu Leu Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln
1 5 10 15

<210> 293
<211> 15
<212> PRT
<213> Homo sapiens

<400> 293

Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe Val Tyr Cys
1 5 10 15

<210> 294
<211> 15
<212> PRT
<213> Homo sapiens

<400> 294

Arg His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp
1 5 10 15

<210> 295
<211> 15
<212> PRT
<213> Homo sapiens

<400> 295

Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala
1 5 10 15

<210> 296
<211> 15
<212> PRT

<213> Homo sapiens

<400> 296

Arg Gly Lys Leu Ala Arg Ala Ser Gly Asn Tyr Ala Thr Val Ile
1 5 10 15

<210> 297
<211> 15
<212> PRT
<213> Homo sapiens

<400> 297

Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys
1 5 10 15

<210> 298
<211> 15
<212> PRT
<213> Homo sapiens

<400> 298

Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val
1 5 10 15

<210> 299
<211> 15
<212> PRT
<213> Homo sapiens

<400> 299

Glu His Pro Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro
1 5 10 15

<210> 300
<211> 15
<212> PRT
<213> Homo sapiens

<400> 300

Thr Glu Leu Phe Ile Ala Ala Glu Gly Ile His Thr Gly Gln Phe
1 5 10 15

<210> 301
<211> 15
<212> PRT
<213> Homo sapiens

<400> 301

Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn Ile Gly

1 5 10 15

<210> 302
<211> 15
<212> PRT
<213> Homo sapiens

<400> 302

Lys Ala Gln Leu Asn Ile Gly Asn Val Leu Pro Val Gly Thr Met
1 5 10 15

<210> 303
<211> 15
<212> PRT
<213> Homo sapiens

<400> 303

Ile Gly Asn Val Leu Pro Val Gly Thr Met Pro Glu Gly Thr Ile
1 5 10 15

<210> 304
<211> 15
<212> PRT
<213> Homo sapiens

<400> 304

Gly Thr Met Pro Glu Gly Thr Ile Val Cys Cys Leu Glu Glu Lys
1 5 10 15

<210> 305
<211> 15
<212> PRT
<213> Homo sapiens

<400> 305

Ile Ser His Asn Pro Glu Thr Lys Lys Thr Arg Val Lys Leu Pro
1 5 10 15

<210> 306
<211> 15
<212> PRT
<213> Homo sapiens

<400> 306

Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala
1 5 10 15

<210> 307
<211> 15

<212> PRT
<213> Homo sapiens

<400> 307

Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Pro Arg Val Arg
1 5 10 15

<210> 308
<211> 15
<212> PRT
<213> Homo sapiens

<400> 308

Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val Glu His Pro
1 5 10 15

<210> 309
<211> 15
<212> PRT
<213> Homo sapiens

<400> 309

His Gln His Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp Ala Pro
1 5 10 15

<210> 310
<211> 15
<212> PRT
<213> Homo sapiens

<400> 310

Arg Arg Thr Gly Arg Leu Arg Gly Thr Lys Thr Val Gln Glu Lys
1 5 10 15

<210> 311
<211> 15
<212> PRT
<213> Homo sapiens

<400> 311

Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala
1 5 10 15

<210> 312
<211> 15
<212> PRT
<213> Homo sapiens

<400> 312

Gly Val Ala Met Asn Pro Val Glu His Pro Phe Gly Gly Gly Asn
1 5 10 15

<210> 313
<211> 15
<212> PRT
<213> Homo sapiens

<400> 313

His Gly Tyr Ile Lys Gly Ile Val Lys Asp Ile Ile His Asp Pro
1 5 10 15

<210> 314
<211> 15
<212> PRT
<213> Homo sapiens

<400> 314

Gly Ser Val Phe Arg Ala His Val Lys His Arg Lys Gly Ala Ala
1 5 10 15

<210> 315
<211> 15
<212> PRT
<213> Homo sapiens

<400> 315

Ser Val Phe Arg Ala His Val Lys His Arg Lys Gly Ala Ala Arg
1 5 10 15

<210> 316
<211> 15
<212> PRT
<213> Homo sapiens

<400> 316

Ser Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys
1 5 10 15

<210> 317
<211> 15
<212> PRT
<213> Homo sapiens

<400> 317

Gly Ala Pro Leu Ala Lys Val Val Phe Arg Asp Pro Tyr Arg Phe
1 5 10 15

<210> 318

<211> 15
<212> PRT
<213> Homo sapiens

<400> 318

Met Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val
1 5 10 15

<210> 319
<211> 15
<212> PRT
<213> Homo sapiens

<400> 319

Gly Arg Val Ile Arg Gly Gln Arg Lys Gly Ala Gly Ser Val Phe
1 5 10 15

<210> 320
<211> 15
<212> PRT
<213> Homo sapiens

<400> 320

Lys Asp Ile Ile His Asp Pro Gly Arg Gly Ala Pro Leu Ala Lys
1 5 10 15

<210> 321
<211> 15
<212> PRT
<213> Homo sapiens

<400> 321

Pro Gly Asp Arg Gly Lys Leu Ala Arg Ala Ser Gly Asn Tyr Ala
1 5 10 15

<210> 322
<211> 15
<212> PRT
<213> Homo sapiens

<400> 322

Asn Arg Ala Val Val Gly Val Val Ala Gly Gly Gly Arg Ile Asp
1 5 10 15

<210> 323
<211> 15
<212> PRT
<213> Homo sapiens

<400> 323

Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp Ala Pro Ala Gly Arg
1 5 10 15

<210> 324
<211> 15
<212> PRT
<213> Homo sapiens

<400> 324

Lys Val Val Phe Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu
1 5 10 15

<210> 325
<211> 15
<212> PRT
<213> Homo sapiens

<400> 325

Arg Asp Pro Tyr Arg Phe Lys Lys Arg Thr Glu Leu Phe Ile Ala
1 5 10 15

<210> 326
<211> 15
<212> PRT
<213> Homo sapiens

<400> 326

Thr Gly Gln Phe Val Tyr Cys Gly Lys Lys Ala Gln Leu Asn Ile
1 5 10 15

<210> 327
<211> 15
<212> PRT
<213> Homo sapiens

<400> 327

Gly Thr Ile Val Cys Cys Leu Glu Glu Lys Pro Gly Asp Arg Gly
1 5 10 15

<210> 328
<211> 15
<212> PRT
<213> Homo sapiens

<400> 328

Glu His Pro Phe Gly Gly Gly Asn His Gln His Ile Gly Lys Pro
1 5 10 15

<210> 329
<211> 15
<212> PRT
<213> Homo sapiens

<400> 329

Gly Asn Tyr Ala Thr Val Ile Ser His Asn Pro Glu Thr Lys Lys
1 5 10 15

<210> 330
<211> 15
<212> PRT
<213> Homo sapiens

<400> 330

Lys Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro
1 5 10 15

<210> 331
<211> 15
<212> PRT
<213> Homo sapiens

<400> 331

Val Lys His Arg Lys Gly Ala Ala Arg Leu Arg Ala Val Asp Phe
1 5 10 15

<210> 332
<211> 15
<212> PRT
<213> Homo sapiens

<400> 332

Pro Glu Thr Lys Lys Thr Arg Val Lys Leu Pro Ser Gly Ser Lys
1 5 10 15

<210> 333
<211> 15
<212> PRT
<213> Homo sapiens

<400> 333

Tyr His Lys Tyr Lys Ala Lys Arg Asn Cys Trp Pro Arg Val Arg
1 5 10 15

<210> 334
<211> 15
<212> PRT
<213> Homo sapiens

<400> 334

Lys Ala Lys Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met
1 5 10 15

<210> 335
<211> 15
<212> PRT
<213> Homo sapiens

<400> 335

Arg Asn Cys Trp Pro Arg Val Arg Gly Val Ala Met Asn Pro Val
1 5 10 15

<210> 336
<211> 15
<212> PRT
<213> Homo sapiens

<400> 336

Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg Gly Thr Lys Thr
1 5 10 15

<210> 337
<211> 15
<212> PRT
<213> Homo sapiens

<400> 337

Val Phe Arg Ala His Val Lys His Arg Lys Gly Ala Ala Arg Leu
1 5 10 15

<210> 338
<211> 15
<212> PRT
<213> Homo sapiens

<400> 338

Pro Gly Arg Gly Ala Pro Leu Ala Lys Val Val Phe Arg Asp Pro
1 5 10 15

<210> 339
<211> 15
<212> PRT
<213> Homo sapiens

<400> 339

Ala Pro Leu Ala Lys Val Val Phe Arg Asp Pro Tyr Arg Phe Lys
1 5 10 15

<210> 340
<211> 15
<212> PRT
<213> Homo sapiens

<400> 340

Arg Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala
1 5 10 15

<210> 341
<211> 15
<212> PRT
<213> Homo sapiens

<400> 341

Val Lys Leu Pro Ser Gly Ser Lys Lys Val Ile Ser Ser Ala Asn
1 5 10 15

<210> 342
<211> 15
<212> PRT
<213> Homo sapiens

<400> 342

Lys Lys Val Ile Ser Ser Ala Asn Arg Ala Val Val Gly Val Val
1 5 10 15

<210> 343
<211> 15
<212> PRT
<213> Homo sapiens

<400> 343

Ser Ser Ala Asn Arg Ala Val Val Gly Val Val Ala Gly Gly Gly
1 5 10 15

<210> 344
<211> 15
<212> PRT
<213> Homo sapiens

<400> 344

Val Ala Gly Gly Gly Arg Ile Asp Lys Pro Ile Leu Lys Ala Gly
1 5 10 15

<210> 345
<211> 15
<212> PRT
<213> Homo sapiens

<400> 345

Leu Lys Ala Gly Arg Ala Tyr His Lys Tyr Lys Ala Lys Arg Asn
1 5 10 15

<210> 346
<211> 15
<212> PRT
<213> Homo sapiens

<400> 346

His Ile Gly Lys Pro Ser Thr Ile Arg Arg Asp Ala Pro Ala Gly
1 5 10 15

<210> 347
<211> 15
<212> PRT
<213> Homo sapiens

<400> 347

Ile Arg Arg Asp Ala Pro Ala Gly Arg Lys Val Gly Leu Ile Ala
1 5 10 15

<210> 348
<211> 15
<212> PRT
<213> Homo sapiens

<400> 348

Gly Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu
1 5 10 15

<210> 349
<211> 15
<212> PRT
<213> Homo sapiens

<400> 349

Arg Lys Val Gly Leu Ile Ala Ala Arg Arg Thr Gly Arg Leu Arg
1 5 10 15

<210> 350
<211> 15
<212> PRT
<213> Homo sapiens

<400> 350

Arg Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile
1 5 10 15