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(54) Title: POPULATION-BASED IMMUNOGENIC PEPTIDE IDENTIFICATION PLATFORM

(57) Abstract: The disclosurerelates to methods of identifying fragments of a polypeptide that are immunogenic for a specific human subject, methods of preparing pharmaceutical compositions comprising such polypeptide fragments, pharmaceutical compositions comprising such polypeptide fragments, and methods of treatment using such compositions. The methods comprise identifying a fragment of the polypeptide that binds to multiple HLA of individual subjects.

POPULATION-BASED IMMUNOGENIC PEPTIDE IDENTIFICATION PLATFORM

Field

The disclosure relates to methods of predicting whether a polypeptide is immunogenic for a specific human subject, methods of identifying fragments of a polypeptide that are immunogenic for a specific human subject, methods of preparing precision pharmaceutical compositions or kits comprising such polypeptide fragments, human subject-specific pharmaceutical compositions comprising such polypeptide fragments, and methods of treatment using such compositions.

Background

For decades, scientists have assumed that chronic diseases were beyond the reach of a person's natural defences. Recently, however, significant tumor regressions observed in individuals treated with antibodies that block immune inhibitory molecules have accelerated the field of cancer immunotherapy. These clinical findings demonstrate that re-activation of existing T cell responses results in meaningful clinical benefit for individuals. These advances have renewed enthusiasm for developing cancer vaccines that induce tumor specific T cell responses.

Despite the promise, current immunotherapy is effective only in a fraction of individuals. In addition, most cancer vaccine trials have failed to demonstrate statistically significant efficacy because of a low rate of tumor regression and antitumor T cell responses in individuals. Similar failures were reported with therapeutic and preventive vaccines that sought to include T cell responses in the fields of HIV and allergy. There is a need to overcome the clinical failures of immunotherapies and vaccines.

Summary

In antigen presenting cells (APC) protein antigens are processed into peptides. These peptides bind to human leukocyte antigen molecules (HLAs) and are presented on the cell surface as peptide-HLA complexes to T cells. Different individuals express different HLA molecules and different HLA molecules present different peptides. Therefore, according to the state of the

art, a peptide, or a fragment of a larger polypeptide, is identified as immunogenic for a specific human subject if it is presented by a HLA molecule that is expressed by the subject. In other words, the state of the art describes immunogenic peptides as HLA-restricted epitopes. However, HLA restricted epitopes induce T cell responses in only a fraction of individuals who express the HLA molecule. Peptides that activate a T cell response in one individual are inactive in others despite HLA allele matching. Therefore, it was unknown how an individual's HLA molecules present the antigen-derived epitopes that positively activate T cell responses.

As provided herein multiple HLA expressed by an individual need to present the same peptide in order to trigger a T cell response. Therefore the fragments of a polypeptide antigen that are immunogenic for a specific individual are those that can bind to multiple class I (activate cytotoxic T cells) or class II (activate helper T cells) HLAs expressed by that individual.

Accordingly, in a first aspect the disclosure provides a method of predicting the cytotoxic T cell response rate and/or the helper T cell response rate of a specific or target human population to administration of a polypeptide, or to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, the method comprising

(i) selecting or defining a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and/or HLA class II genotype;

(ii) determining for each subject in the model human population whether the polypeptide or polypeptides together comprise

(a) at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; and/or

(b) at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

(iii) predicting

A. the cytotoxic T cell response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(a) predicts a higher cytotoxic T cell response rate in said human population; and/or

B. the helper T cell response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(b) predicts a higher helper T cell response rate in said human population.

The disclosure further provides a method of predicting the clinical response rate of a specific or target human population to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, the method comprising

(i) selecting or defining a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype;

(ii) determining

(a) for each subject in the model human population whether the one or more active ingredient polypeptides together comprise at least two different amino acid sequences each of which is a T cell epitope capable of binding to at least two HLA class I molecules of the subject, optionally wherein the at least two different amino acid sequences are comprised in the amino acid sequence of two different polypeptide antigens targeted by the active ingredient polypeptide(s);

(b) in the model population the mean number of target polypeptide antigens that comprise at least one amino acid sequence that is

A. a T cell epitope capable of binding to at least three HLA class I molecules of the individual subjects of the model population; and

B. comprised in the amino acid sequence of the active ingredient polypeptide(s); and/or

(c) in the model population the mean number of expressed target polypeptide antigens that comprise at least one amino acid sequence that is

A. a T cell epitope capable of binding to at least three HLA class I molecules of the individual subjects of the model population; and

B. comprised in the amino acid sequence of the active ingredient polypeptide(s); and

(iii) predicting the clinical response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(a), or a higher mean number of target polypeptides in step (ii)(b), or or a higher mean number of expressed target polypeptides in step (ii)(c) predicts a higher clinical response rate in said human population.

The disclosure further provides methods of treatment of a human subject in need thereof, the method comprising administering to the subject a polypeptide, pharmaceutical composition or kit of the polypeptides of a panel of polypeptides that has been identified or selected based on ther predicted immune or cinical response rate determined as described above; their use in a method of treatment of a relevant human subject; and their use in the manufacture of a medicament for treating a relevant subject.

The disclosure also provides a method of designing or preparing a polypeptide, or a polynucleic acid that encodes a polypeptide, for use in a method of inducing an immune response in a subject of a specific or target human population, the method comprising

(i) selecting or defining

(a) a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and/or by HLA class II genotype; and/or

(b) a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and one relevant model human population comprising a plurality of subjects each defined by HLA class II genotype;

(ii) identifying a fragment of up to 50 consecutive amino acids of a target polypeptide antigen that comprises or consists of

A. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of the individual subjects;

B. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of the individual subjects; or

C. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of the individual subjects and a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of the individual subjects;

(iii) if the polypeptide fragment selected in step (ii) consists of an amino acid sequence that is an HLA class I–binding epitope, optionally selecting a longer fragment of the target polypeptide antigen, which longer fragment comprises or consists of an amino acid sequence that

D. comprises the fragment selected in step (ii); and

E. is an HLA class II molecule-binding T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three, or the most possible HLA class II molecules of the individual subjects; and

(iv) designing or preparing a polypeptide, or a polynucleic acid that encodes a polypeptide that comprises or consists of one or more polypeptide fragments identified in step (ii) or step (iii), optionally wherein the polypeptide fragment is flanked at the N and/or C terminus by additional amino acids that are not part of the sequence of the target polypeptide antigen.

The disclosure provides a method of inducing an immune response in a subject of a specific or target human population, the method comprising designing or preparing a polypeptide, a panel of polypeptides, a polynucleic acid encoding a polypeptide, or a pharmaceutical composition or

kit for use in said specific or target human population as described above and administering the polypeptide(s), polynucleic acid, pharmaceutical composition or the active ingredient polypeptides of the kit to the subject.

The disclosure provides a polypeptide, panel of polypeptides, polynucleic acid, pharmaceutical composition or kit for use in a method of inducing an immune response in a subject of a specific or target human population, wherein the polypeptide, panel of polypeptides, polynucleic acid, pharmaceutical composition or kit is designed or prepared as described above for use in said specific or target human population, and wherein the composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

This disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method of inducing an immune response in a human subject, wherein the pharmaceutical composition, panel of polypeptides or kit comprises as active ingredients a first and a second and optionally one or more additional peptides, wherein each peptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of human subjects, wherein the T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method of inducing an immune response in a human subject, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first region and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of human subjects, wherein the T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer in a subject in need thereof, wherein the pharmaceutical composition,

panel of polypeptides or kit comprises as active ingredients a first and a second peptide and optionally one or more additional peptides, wherein each peptide comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each said T cell epitope at least 10% of human subjects having cancer both

i. express a tumor associated antigen selected from the antigens listed in Table 2 or Table 5 below that comprises said T cell epitope; and

ii. have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional peptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer in a subject in need thereof, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each said T cell epitope at least 10% of human subjects having cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 or Table 5 below that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer selected from colorectal, breast, ovarian, melanoma, non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma in a subject in need thereof, wherein the pharmaceutical composition, panel of

polypeptides or kit comprises as active ingredients a first and a second peptide and optionally one or more additional polypeptides, wherein each peptide comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each said T cell epitope at least 10% of human subjects having said cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 or Table 5 below that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional peptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer selected from colorectal, breast, ovarian, melanoma, non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma in a subject in need thereof, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each said T cell epitope at least 10% of human subjects having said cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 or Table 5 below that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional polypeptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

The disclosure provides a method of treatment of a human subject in need thereof, the method comprising administering to the subject a polypeptide, a panel of polypeptides, a pharmaceutical composition or the active ingredient polypeptides of a kit described above, wherein the subject has been determined to express at least three HLA class I molecules and/or at least three HLA class II molecules capable of binding to the polypeptide or to one or more of the active ingredient poypeptides of the pharmaceutical composition or kit.

In a further aspect the invention provides a system comprising

(a) a storage module configured to store data comprising the class I and/or class II HLA genotypes of each subject of a model population of human subjects; and the amino acid sequence of one or more test polypeptides; wherein the model population is representative of a test target human population; and

(b) a computation module configured to identify and/or quantify the amino acid sequences in the one or more test polypeptides that are capable of binding to multiple class I HLA molecules of each subject in the model population and/or the amino acid sequences in the one or more test polypeptides that are capable of binding to multiple class II HLA molecules of each subject in the model population.

The disclosure will now be described in more detail, by way of example and not limitation, and by reference to the accompanying drawings. Many equivalent modifications and variations will be apparent, to those skilled in the art when given this disclosure. Accordingly, the exemplary embodiments of the disclosure set forth are considered to be illustrative and not limiting. Various changes to the described embodiments may be made without departing from the scope of the disclosure. All documents cited herein, whether supra or infra, are expressly incorporated by reference in their entirety.

The present disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or is stated to be expressly avoided. As used in this specification and the appended claims, the singular forms “a”, “an”, and

"the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a peptide" includes two or more such peptides.

Section headings are used herein for convenience only and are not to be construed as limiting in any way.

Description of the Figures

Fig. 1

ROC curve of HLA restricted PEPI biomarkers.

Fig. 2

ROC curve of ≥1 PEPI3+ Test for the determination of the diagnostic accuracy.

Fig. 3

Distribution of HLA class I PEPI3+ compared to CD8+ T cell responses measured by a state of art assay among peptide pools used in the CD8+ T cell response assays. A: HLA class I restricted PEPI3+s. The 90% Overall Percent of Agreement (OPA) among the T cell responses and PEPI3+ peptides demonstrate the utility of the disclosed peptides for prediction of vaccine induced T cell response set of individuals. B: Class I HLA restricted epitopes (PEPI1+). The OPA between predicted epitopes and CD8+ T cell responses was 28% (not statistically significant). Darkest grey: True positive (TP), both peptide and T cell responses were detected; Light grey: False negative (FN), only T cell responses were detected; Lightest grey: False positive (FP), only peptide were detected; Dark grey: True negative (TN): neither peptides nor T cell responses were detected.

Fig. 4

Distribution of HLA class II PEPIs compared to CD4+ T cell responses measured by a state of art assay among peptide pools used in the assays. A: HLA class II restricted PEPI4+s. 67% OPA between PEPI4+ and CD4+ T-cell responses (p=0.002). B: The class II HLA restricted epitopes. OPA between class II HLA restricted epitopes and CD4+ T cell responses was 66% (not statistically significant). Darkest grey: True positive (TP), both peptide and T cell responses were detected; Light grey: False negative (FN), only T cell responses were detected; Lightest grey:

False positive (FP), only peptide were detected; Dark grey: True negative (TN): neither peptides nor T cell responses were detected.

Fig. 5

Multiple HLA binding peptides that define the HPV-16 LPV vaccine specific T cell response set of 18 VIN-3 and 5 cervical cancer patients. HLA class I restricted PEPI3 counts (A and B) and HLA class II restricted PEPI3 counts (C and D) derived from LPV antigens of each patient. Light grey: immune responders measured after vaccination in the clinical trial; Dark grey: Immune non-responders measured after vaccination in the clinical trial. Results show that ≧3 HLA class I binding peptides predict the CD8+ T cell reactivity and ≧4 HLA class II binding peptides predict the CD4+ T cell reactivity.

Fig. 6

The multiple HLA class I binding peptides that define the HPV vaccine specific T cell response set of 2 patients. A: Four HPV antigens in the HPV vaccine. Boxes represent the length of the amino acid sequences from the N terminus to the C terminus. B: Process to identify the multiple HLA binding peptides of two patients: HLA sequences of the patients labelled as 4-digit HLA genotype right from the patient's ID. The location of the 1st amino acid of the 54 and 91 epitopes that can bind to the patient 12-11 and patient 14-5 HLAs (PEPI1+) respectively are depicted with lines. PEPI2 represents the peptides selected from PEPI1+s that can bind to multiple HLAs of a patient (PEPI2+). PEPI3 represent peptides that can bind to ≧3 HLAs of a patient (PEPI3+). PEPI4 represent peptides that can bind to ≧4 HLAs of a patient (PEPI4+). PEPI5 represent peptides that can bind to ≧5 HLAs of a patient (PEPI5+). PEPI6 represent peptides that can bind to 6 HLAs of a patient (PEPI6). C: The DNA vaccine specific PEPI3+ set of two patients characterizes their vaccine specific T cell responses.

Fig. 7

Correlation between the ≧1 PEPI3+ Score and CTL response rates of peptide targets determined in clinical trials.

Fig. 8

Correlation between the ≧1 PEPI3+ Score and the clinical Immune Response Rate (IRR) of immunotherapy vaccines. Dashed lines: 95% confidence band.

Fig 9

Correlation between the ≧2 PEPI3+ Score and Disease Control Rate (DCR) of immunotherapy vaccines. Dashed lines: 95% confidence band.

Fig. 10

HLA map of the Rindopepimut on the HLA alleles of the subjects in the Model Population.

Fig. 11

Probability of vaccine antigen expression in the XYZ patient's tumor cells. There is over 95% probability that 5 out of the 12 target antigens in the vaccine regimen is expressed in the patient's tumor. Consequently, the 12 peptide vaccines together can induce immune responses against at least 5 ovarian cancer antigens with 95% probability (AGP95). It has 84% probability that each peptide will induce immune responses in the XYZ patient. AGP50 is the mean (expected value) =7.9 (it is a measure of the effectiveness of the vaccine in attacking the tumor of XYZ patient).

Fig. 12

MRI findings of patient XYZ treated with personalised (PIT) vaccine. This late stage, heavily pretreated ovarian cancer patient had an unexpected objective response after the PIT vaccine treatment. These MRI findings suggest that PIT vaccine in combination with chemotherapy significantly reduced her tumor burden. The patient now continues the PIT vaccine treatment.

Fig. 13

Probability of vaccine antigen expression in the ABC patient's tumor cells. There is over 95% probability that 4 out of the 13 target antigens in the vaccine is expressed in the patient's tumor. Consequently, the 12 peptide vaccines together can induce immune responses against at least 4 breast cancer antigens with 95% probability (AGP95). It has 84% probability that each peptide will induce immune responses in the ABC patient. AGP50 is the mean (expected value) of the discrete probability distribution = 6.45 (it is a measure of the effectiveness of the vaccine in attacking the tumor of ABC patient).

Fig. 14

Peptide hotspot analysis example: PRAME antigen hotspot on 433 patients of the Model Population. On the y axis are the 433 patients of the Model Population, on the x axis is the amino acid sequence of the PRAME antigen (CTA). Each data point represents a PEPI presented by ≧3 HLA class I of one patient starting at the specified amino acid position. The two most frequent PEPIs (called bestEPIs) of the PRAME antigen are highlighted in dark gray (peptide hotspots = PEPI Hotspots).

Fig. 15

CTA Expression Curve calculated by analyzing expression frequency data of tumor specific antigens (CTAs) in human breast cancer tissues. (No cell line data were included.)

Fig. 16

Antigen expression distribution for breast cancer based on the calculation of multi-antigen responses from expression frequencies of the selected 10 different CTAs. A: non-cumulative distribution to calculate the expected value for the number of expressed antigens (AG50). This value shows that probably 6.14 vaccine antigens will be expressed by breast tumor cells. B: cumulative distribution curve of the minimum number of expressed antigens (CTA expression curve). This shows that minimum 4 vaccine antigens will be expressed with 95% probability in breast cancer cell (AG95).

Fig. 17

PEPI representing antigens: breast cancer vaccine-specific CTA antigens with ≥1 PEPI, called as "AP") distribution within the Model Population (n=433) for breast cancer vaccine. A: non-cumulative distribution of AP where the average number of APs is: AP50=5.30, meaning that in average almost 6 CTAs will have PEPIs in the Model Population. B: cumulative distribution curve of the minimum number of APs in the Model Population (n=433). This shows that at least one vaccine antigen will have PEPIs in 95% of the Model Population (n=433) (AP95=1).

Fig. 18

PEPI represented expressed antigen (breast cancer vaccine-specific CTA antigens expressed by the tumor, for which ≥1 PEPI is predicted, called as "AGP") distribution within the model population (n=433) calculated with CTA expression rates for breast cancer. A: non-cumulative

distribution of AGP where the expected value for number expressed CTAs represented by PEPI is AGP50=3.37. AGP50 is a measure of the effectiveness of the disclosed breast cancer vaccine in attacking breast tumor in an unselected patient population. AGP50 = 3.37 means that at least 3 CTAs from the vaccine will probably be expressed by the breast tumor cells and present PEPIs in the Model Population. B: cumulative distribution curve of the minimum number of AGPs in the Model Population (n=433) shows that at least 1 of the vaccine CTAs will present PEPIs in 92% of the population and the remaining 8% of the population will likely have no AGP at all (AGP95=0, AGP92=1).

Fig. 19

CTA Expression Curve calculated by analyzing expression frequency data of tumor specific antigens (CTAs) in human colorectal cancer tissues. (No cell line data were included.)

Fig. 20

Antigen expression distribution for colorectal cancer based on the calculation of multi-antigen responses from expression frequencies of the selected 7 different CTAs. A: non-cumulative distribution to calculate the expected vale for the number of expressed vaccine antigens in colorectal cancers (AG50). This value shows that probably 4.96 vaccine antigens will be expressed by colorectal tumor cells. B: cumulative distribution curve of the minimum number of expressed antigens (CTA expression curve). This shows that minimum 3 antigens will be expressed with 95% probability in the colorectal cancer cell (AG95).

Fig. 21

PEPI represented antigen (colorectal cancer vaccine-specific CTA antigens for which ≥1 PEPI is predicted. Called as "AP") distribution within the model population (n=433) for colorectal cancer. A: non-cumulative distribution of AP where the average number of APs is: AP50=4.73, meaning that in average 5 CTAs will be represented by PEPIs in the model population B: cumulative distribution curve of the minimum number of APs in the model population (n=433). This shows that 2 or more antigens will be represented by PEPIs in 95% of the model population (n=433) (AP95=2).

Fig. 22

PEPI represented expressed antigen (colorectal cancer vaccine-specific CTA antigens expressed by the tumor, for which ≥1 PEPI is predicted. Called as "AGP") distribution within the model population (n=433) calculated with CTA expression rates for colorectal cancer. A: non-cumulative distribution of AGP where the expected value for number expressed CTAs represented by PEPI is AGP50=2.54. AGP50 is a measure of the effectiveness of the disclosed colorectal cancer vaccine in attacking colorectal tumors in an unselected patient population. AGP50 = 2.54 means that at least 2-3 CTAs from the vaccine will probably be expressed by the colorectal tumor cells and present PEPIs in the Model Population. B: cumulative distribution curve of the minimum number of AGPs in the Model Population (n=433) shows that at least 1 of the vaccine CTAs will be expressed and also present PEPIs in 93% of the population (AGP93=1).

Fig 23

Schematic showing exemplary positions of amino acids in overlapping HLA class I- and HLA class-II binding epitopes in a 30-mer peptide.

Fig. 24

Antigenicity of PolyPEPI1018 CRC Vaccine in a general population. The antigenicity of PolyPEPI1018 in a subject is determined by the AP count, which indicates the number of vaccine antigens that induce T cell responses in a subject. The AP count of PolyPEPI1018 was determined in each of the 433 subjects in the Model Population using the PEPI Test, and the AP50 count was then calculated for the Model Population. The AP50 of PolyPEPI1018 in the Model Population is 4.73. The mean number of immunogenic antigens (i.e., antigens with ≥1 PEPI) in PolyPEPI1018 in a general population is 4.73. Abbreviations: AP = antigens with ≥1 PEPI. Left Panel: Cumulative distribution curve. Right Panel: Distinct distribution curve.

Fig. 25

Effectiveness of PolyPEPI1018 CRC Vaccine in a general population. Vaccine induced T cells can recognize and kill tumor cells if a PEPI in the vaccine is presented by the tumor cell. The number of AGPs (expressed antigens with PEPI) is an indicator of vaccine effectiveness in an individual, and is dependent on both the potency and antigenicity of PolyPEPI1018. The mean number of immunogenic CTAs (i.e., AP [expressed antigens with ≥1 PEPI]) in PolyPEPI1018 is

2.54 in the Model Population. The likelihood that PolyPEPI1018 induces T cell responses against multiple antigens in a subject (i.e., mAGP) in the Model Population is 77%.

Description of the Sequences

SEQ ID NOs: 1 to 20 set forth 9 mer T cell epitopes described in Table 30.

SEQ ID NOs: 21 to 40 set forth 9 mer T cell epitopes described in Table 33.

SEQ ID NOs: 41-71 (81 to 111) set forth the breast cancer vaccine peptides set forth in Table 31.

SEQ ID NOs 72-102 (112 to 142) set forth the colorectal cancer vaccine peptides set forth in Table 34.

SEQ ID NOs 103-115 (159 to 171) set forth the additional peptide sequences described in Table 17.

SEQ ID NOs: 116-128 (362 to 374) set forth personalised vaccine peptides designed for patient XYZ described in Table 26.

SEQ ID NOs: 129-140 (375 to 386) set forth personalised vaccine peptides designed for patient ABC described in Table 29.

SEQ ID NOs: 141-188 (387 to 434) set forth further 9 mer T cell epitopes described in Table 41.

Detailed Description

HLA Genotypes

HLAs are encoded by the most polymorphic genes of the human genome. Each person has a maternal and a paternal allele for the three HLA class I molecules (HLA-A*, HLA-B*, HLA-C*) and four HLA class II molecules (HLA-DP*, HLA-DQ*, HLA-DRB1*, HLA-DRB3*/4*/5*). Practically, each person expresses a different combination of 6 HLA class I and 8 HLA class II molecules that present different epitopes from the same protein antigen. The function of HLA molecules is to regulate T cell responses. However up to date it was unknown how the HLAs of a person regulate T cell activation.

The nomenclature used to designate the amino acid sequence of the HLA molecule is as follows: gene name*allele:protein number, which, for instance, can look like: HLA-A*02:25. In

this example, "02" refers to the allele. In most instances, alleles are defined by serotypes – meaning that the proteins of a given allele will not react with each other in serological assays. Protein numbers ("25" in the example above) are assigned consecutively as the protein is discovered. A new protein number is assigned for any protein with a different amino acid sequence (e.g. even a one amino acid change in sequence is considered a different protein number). Further information on the nucleic acid sequence of a given locus may be appended to the HLA nomenclature, but such information is not required for the methods described herein.

The HLA class I genotype or HLA class II genotype of an individual may refer to the actual amino acid sequence of each class I or class II HLA of an individual, or may refer to the nomenclature, as described above, that designates, minimally, the allele and protein number of each HLA gene. An HLA genotype may be obtained or determined using any suitable method. For example, the sequence may be determined via sequencing the HLA gene loci using methods and protocols known in the art. Alternatively, the HLA set of an individual may be stored in a database and accessed using methods known in the art.

HLA-epitope binding

A given HLA of a subject will only present to T cells a limited number of different peptides produced by the processing of protein antigens in an APC. As used herein, "display" or "present", when used in relation to HLA, references the binding between a peptide (epitope) and an HLA. In this regard, to "display" or "present" a peptide is synonymous with "binding" a peptide.

As used herein, the term "epitope" or "T cell epitope" refers to a sequence of contiguous amino acids contained within a protein antigen that possess a binding affinity for (is capable of binding to) one or more HLAs. An epitope is HLA- and antigen-specific (HLA-epitope pairs, predicted with known methods), but not subject specific. An epitope, a T cell epitope, a polypeptide, a fragment of a polypeptide or a composition comprising a polypeptide or a fragment thereof is "immunogenic" for a specific human subject if it is capable of inducing a T cell response (a cytotoxic T cell response or a helper T cell response) in that subject. In some

cases the helper T cell response is a Th1-type helper T cell response. In some cases an epitope, a T cell epitope, a polypeptide, a fragment of a polypeptide or a composition comprising a polypeptide or a fragment thereof is "immunogenic" for a specific human subject if it is more likely to induce a T cell response or immune response in the subject than a different T cell epitope (or in some cases two different T cell epitopes each) capable of binding to just one HLA molecule of the subject.

The terms "T cell response" and "immune response" are used herein interchangeably, and refer to the activation of T cells and/or the induction of one or more effector functions following recognition of one or more HLA-epitope binding pairs. In some cases an "immune response" includes an antibody response, because HLA class II molecules stimulate helper responses that are involved in inducing both long lasting CTL responses and antibody responses. Effector functions include cytotoxicity, cytokine production and proliferation. According to the present disclosure, an epitope, a T cell epitope, or a fragment of a polypeptide is immunogenic for a specific subject if it is capable of binding to at least two, or in some cases at least three, class I or at least two, or in some cases at least three or at least four class II HLAs of the subject.

For the purposes of this disclosure we have coined the term "personal epitope", or "PEPI" to distinguish subject specific epitopes from HLA specific epitopes. A "PEPI" is a fragment of a polypeptide consisting of a sequence of contiguous amino acids of the polypeptide that is a T cell epitope capable of binding to one or more HLA class I molecules of a specific human subject. In other cases a "PEPI" is a fragment of a polypeptide consisting of a sequence of contiguous amino acids of the polypeptide that is a T cell epitope capable of binding to one or more HLA class II molecules of a specific human subject. In other words a "PEPI" is a T cell epitope that is recognised by the HLA set of a specific individual. In contrast to an "epitope", PEPIs are specific to an individual because different individuals have different HLA molecules which each bind to different T cell epitopes.

"PEPI1" as used herein refers to a peptide, or a fragment of a polypeptide, that can bind to one HLA class I molecule (or, in specific contexts, HLA class II molecule) of an individual.

"PEPI1+" refers to a peptide, or a fragment of a polypeptide, that can bind to one or more HLA class I molecule of an individual.

"PEPI2" refers to a peptide, or a fragment of a polypeptide, that can bind to two HLA class I (or II) molecules of an individual. "PEPI2+" refers to a peptide, or a fragment of a polypeptide, that can bind to two or more HLA class I (or II) molecules of an individual, i.e. a fragment identified according to a method of the disclosure.

"PEPI3" refers to a peptide, or a fragment of a polypeptide, that can bind to three HLA class I (or II) molecules of an individual. "PEPI3+" refers to a peptide, or a fragment of a polypeptide, that can bind to three or more HLA class I (or II) molecules of an individual.

"PEPI4" refers to a peptide, or a fragment of a polypeptide, that can bind to four HLA class I (or II) molecules of an individual. "PEPI4+" refers to a peptide, or a fragment of a polypeptide, that can bind to four or more HLA class I (or II) molecules of an individual.

"PEPI5" refers to a peptide, or a fragment of a polypeptide, that can bind to five HLA class I (or II) molecules of an individual. "PEPI5+" refers to a peptide, or a fragment of a polypeptide, that can bind to five or more HLA class I (or II) molecules of an individual.

"PEPI6" refers to a peptide, or a fragment of a polypeptide, that can bind to all six HLA class I (or six HLA class II) molecules of an individual.

Generally speaking, epitopes presented by HLA class I molecules are about nine amino acids long and epitopes presented by HLA class II molecules are about fifteen amino acids long. For the purposes of this disclosure, however, an epitope may be more or less than nine (for HLA Class I) or more or less than fifteen (for HLA Class II) amino acids long, as long as the epitope is capable of binding HLA. For example, an epitope that is capable of binding to class I HLA may be between 7, or 8 or 9 and 9 or 10 or 11 amino acids long. An epitope that is capable of binding to a class II HLA may be between 13, or 14 or 15 and 15 or 16 or 17 amino acids long.

Therefore the disclosure herein includes, for example, a method of predicting whether a polypeptide is immunogenic for a relevant population or cohort of human subjects (e.g., in a model human population) or identifying a fragment of a polypeptide as immunogenic for a

relevant population or cohort of human subjects (e.g., in a model human population), the method comprising the steps of

(i) determining whether the polypeptide comprises:

a. a sequence of 7 to 11 consecutive amino acids that is capable of binding to at least two HLA class I of the subject; or

b. a sequence of 13 to 17 consecutive amino acids that is capable of binding to at least two HLA class II of the subject; and

(ii) predicting that the polypeptide is immunogenic for the subject if the polypeptide comprises at least one sequence that meets the requirements of step (i); or predicting that the polypeptide is not immunogenic for the subject if the polypeptide does not comprise at least one sequence that meets the requirements of step (i); or identifying said consecutive sequence of amino acids as the sequence of a fragment of the polypeptide that is immunogenic for the subject.

Using techniques known in the art, it is possible to determine the epitopes that will bind to a known HLA. Any suitable method may be used, provided that the same method is used to determine multiple HLA-epitope binding pairs that are directly compared. For example, biochemical analysis may be used. It is also possible to use lists of epitopes known to be bound by a given HLA. It is also possible to use predictive or modelling software to determine which epitopes may be bound by a given HLA. Examples are provided in Table 1. In some cases a T cell epitope is capable of binding to a given HLA if it has an IC50 or predicted IC50 of less than 5000 nM, less than 2000 nM, less than 1000 nM, or less than 500 nM.

Table 1. Example software for determining epitope-HLA binding

EPITOPE PREDICTION TOOLS	WEB ADDRESS
BIMAS, NIH	www-bimas.cit.nih.gov/molbio/hla_bind/
PPAPROC, Tubingen Univ.	
MHCPred, Edward Jenner Inst. of Vaccine Res.	
EpiJen, Edward Jenner Inst. of Vaccine Res.	http://www.ddg-pharmfac.net/epijen/EpiJen/EpiJen.htm

NetMHC, Center for Biological Sequence Analysis	http://www.cbs.dtu.dk/services/NetMHC/
SVMHC, Tubingen Univ.	http://abi.inf.uni-tuebingen.de/Services/SVMHC/
SYFPEITHI, Biomedical Informatics, Heidelberg	http://www.syfpeithi.de/bin/MHCServer.dll/EpitopePredictio n.htm
ETK EPITOOLKIT, Tubingen Univ.	http://etk.informatik.uni-tuebingen.de/epipred/
PREDEP, Hebrew Univ. Jerusalem	http://margalit.huji.ac.il/Teppred/mhc-bind/index.html
RANKPEP, MIF Bioinformatics	http://bio.dfci.harvard.edu/RANKPEP/
IEDB, Immune Epitope Database	http://tools.immuneepitope.org/main/html/tcell_tools.html
EPITOPE DATABASES	WEB ADDRESS
MHCBN, Institute of Microbial Technology, Chandigarh, INDIA	http://www.imtech.res.in/raghava/mhcbn/
SYFPEITHI, Biomedical Informatics, Heidelberg	http://www.syfpeithi.de/
AntiJen, Edward Jenner Inst. of Vaccine Res.	http://www.ddg-pharmfac.net/antijen/AntiJen/antijenhomepage.htm
EPIMHC database of MHC ligands, MIF Bioinformatics	http://immunax.dfci.harvard.edu/epimhc/
IEDB, Immune Epitope Database	http://www.iedb.org/

As provided herein T cell epitope presentation by multiple HLAs of an individual is generally needed to trigger a T cell response. Accordingly, the methods of the disclosurecomprise determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to at least two HLA class I molecules or at least two HLA class II (PEPI2+) molecules of a human subject (e.g., in a model human population).

The best predictor of a cytotoxic T cell response to a given polypeptide is the presence of at least one T cell epitope that is presented by three or more HLA class I molecules of an individual (≥1 PEPI3+). Accordingly, in some cases the method comprises determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of a specific human subject. In some cases the method comprises determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to just three HLA class I of a human subject (e.g., in a model human population). A helper T cell response may be predicted by the presence of at least one T cell epitope that is presented by three or more (≥1

PEPI3+) or 4 or more (≥1 PEPI4+) HLA class II of an individual. Therefore in some cases, the method comprises determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to at least three HLA class II of a human subject (e.g., in a model human population). In other cases, the method comprises determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to at least four HLA class II of a human subject. In other cases, the method comprises determining whether a polypeptide has a sequence that is a T cell epitope capable of binding to at just three and/or just four HLA class II of a human subject.

In some cases, the disclosed methods and compositions may be used to predict whether a polypeptide/fragment will induce both a cytotoxic T cell response and a helper T cell response in a human subject. The polypeptide/fragment comprises both an amino acid sequence that is a T cell epitope capable of binding to multiple HLA class I molecules of the subject and an amino acid sequence that is a T cell epitope capable of binding to multiple HLA class II molecules of the subject. The HLA class I-binding and HLA class II-binding epitopes may fully or partially overlap. In some cases such fragments of a polypeptide may be identified by selecting an amino acid sequence that is a T cell epitope capable of binding to multiple (e.g. at least two or at least three) HLA class I molecules of the subject, and then screening one or more longer fragments of the polypeptide that are extended at the N- and/or C-terminus for binding to one or more or the most possible (i.e. when no suitable HLA class II-binding PEPI3+s are available) HLA class II molecules of the subject or of a high percentage of subjects in a population. .

Some subjects may have two HLA alleles that encode the same HLA molecule (for example, two copies for HLA-A*02:25 in case of homozygosity). The HLA molecules encoded by these alleles bind all of the same T cell epitopes. For the purposes of this disclosure "binding to at least two HLA molecules of the subject" as used herein includes binding to the HLA molecules encoded by two identical HLA alleles in a single subject. In other words, "binding to at least two HLA molecules of the subject" and the like could otherwise be expressed as "binding to the HLA molecules encoded by at least two HLA alleles of the subject".

Polypeptide Antigens

As used herein, the term "polypeptide" refers to a full-length protein, a portion of a protein, or a peptide characterized as a string of amino acids. As used herein, the term "peptide" refers to a short polypeptide comprising between 2, or 3, or 4, or 5, or 6, or 7, or 8, or 9, or 10, or 11, or 12, or 13, or 14, or 15 and 10, or 11, or 12, or 13, or 14, or 15, or 20, or 25, or 30, or 35, or 40, or 45, or 50 amino acids.

The terms "fragment" or "fragment of a polypeptide" as used herein refer to a string of amino acids or an amino acid sequence typically of reduced length relative to the or a reference polypeptide and comprising, over the common portion, an amino acid sequence identical to the reference polypeptide. Such a fragment according to the disclosure may be, where appropriate, included in a larger polypeptide of which it is a constituent. In some cases the fragment may comprise the full length of the polypeptide, for example where the whole polypeptide, such as a 9 amino acid peptide, is a single T cell epitope.

In some cases the polypeptide is, or the polypeptide consists of all or part of an antigen that is, expressed by a pathogenic organism (for example, a bacteria or a parasite), a virus, or a cancer cell, that is associated with an autoimmune disorder or response or a disease-associated cell, or that is an allergen, or an ingredient of a medicine or pharmaceutical composition such as a vaccine or immunotherapy composition. In some cases the method of the disclosure comprises an initial step of identifying or selecting a suitable polypeptide, for example a polypeptide as further described below.

The polypeptide or antigen may be expressed in the cells or specifically in diseased cells of the specific or target human population (e.g. a tumor-associated antigen, a polypeptide expressed by a virus, intracellular bacteria or parasite, or the *in vivo* product of a vaccine or immunotherapy composition) or acquired from the environment (e.g. a food, an allergen or a drug). The polypeptide or antigen may be present in a sample taken from a subject of the specific or target human population. Both polypeptide antigens and HLAs can be exactly defined by amino acid or nucleotide sequences and sequenced using methods known in the art.

The polypeptide or antigen may be a cancer- or tumor-associated antigen (TAA). TAAs are proteins expressed in cancer or tumor cells. The cancer or tumour cell may be present in a sample obtained from a subject of the specific or target human population. Examples of TAAs include new antigens (neoantigens) expressed during tumorigenesis, products of oncogenes and tumor suppressor genes, overexpressed or aberrantly expressed cellular proteins (e.g. HER2, MUC1), antigens produced by oncogenic viruses (e.g. EBV, HPV, HCV, HBV, HTLV), cancer testis antigens (CTA)(e.g. MAGE family, NY-ESO) and cell-type-specific differentiation antigens (e.g. MART-1). TAA sequences may be found experimentally, or in published scientific papers, or through publicly available databases, such as the database of the Ludwig Institute for Cancer Research (www.cta.lncc.br/), Cancer Immunity database (cancerimmunity.org/peptide/) and the TANTIGEN Tumor T cell antigen database (cvc.dfci.harvard.edu/tadb/).

In some cases the polypeptide or antigen is not expressed or is minimally expressed in normal healthy cells or tissues, but is expressed (in those cells or tissues) in a high proportion of (with a high frequency in) subjects having a particular disease or condition, such as a type of cancer or a cancer derived from a particular cell type or tissue, for example breast cancer, ovarian cancer or melanoma. A further example is colorectal cancer. Other non-limiting cancer examples include non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma. Alternatively, the polypeptide may be expressed at low levels in normal healthy cells, but at high levels (overexpressed) in diseased (e.g. cancer) cells or in subjects having the disease or condition. In some cases the polypeptide is expressed in, or expressed at a high level relative to normal healthy cells or subjects in, at least 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of such individuals, or of a subject-matched human subpopulation or model or target population. For example the population may be matched to the subject by ethnicity, geographical

location, gender, age, disease, disease type or stage, genotype, or expression of one or more biomarkers.

In some cases the expression frequencies can be determined from published figures and scientific publications. In some cases the method of the disclosure comprises a step of identifying or selecting such a polypeptide.

In some cases the polypeptide is associated with or highly (over-) expressed in cancer cells, or in solid tumors. Exemplary cancers include carcinomas, sarcomas, lymphomas, leukemias, germ cell tumors, or blastomas. The cancer may or may not be a hormone related or dependent cancer (*e.g.*, an estrogen or androgen related cancer). The tumor may be malignant or benign. The cancer may or may not be metastatic.

In some cases the polypeptide is a cancer testis antigens (CTA). CTA are not typically expressed beyond embryonic development in healthy cells. In healthy adults, CTA expression is limited to male germ cells that do not express HLAs and cannot present antigens to T cells. Therefore, CTAs are considered expressional neoantigens when expressed in cancer cells. CTA expression is (i) specific for tumor cells, (ii) more frequent in metastases than in primary tumors and (iii) conserved among metastases of the same patient (Gajewski ed. Targeted Therapeutics in Melanoma. Springer New York. 2012).

The polypeptide may be a mutational neoantigen, which is expressed by a cell, for example a cancer cell, of the individual, but altered from the analogous protein in a normal or healthy cell. In some cases the methods of the disclosure comprise the step of identifying a polypeptide that is a mutational neoantigen, or that is a mutational neoantigen in the specific human subject, or of identifying a neoepitope. For example the neoantigen may be present in a sample obtained from the subject. Mutational neoantigens or neoepitopes can be used to target disease-associated cells, such as cancer cells, that express the neoantigen or a neoantigen comprising the neoepitope. Mutations in a polypeptide expressed by a cell, for example a cell in a sample taken from a subject, can be detected by, for example, sequencing, but the majority do not induce an immune response against the neoantigen-expressing cells. Currently, the identification of mutational neoantigens that do induce an immune response is based on

prediction of mutational HLA restricted epitopes and further *in vitro* testing of the immunogenicity of predicted epitopes in individual's blood specimen. This process is inaccurate, long and expensive.

The identification of mutational epitopes (e.g., neoepitopes) that bind to multiple HLA molecules reproducibly define the immunogenicity of mutational neoantigens. Therefore, in some cases in accordance with the disclosure, the polypeptide is a mutational neoantigen, and the immunogenic fragment of the polypeptide comprises a neoantigen specific mutation (or consists of a neoepitope).

The polypeptide may be a viral protein that is expressed intracellularly. Examples include HPV16 E6, E7; HIV Tat, Rev, Gag, Pol, Env; HTLV-Tax, Rex, Gag, Env, Human herpes virus proteins, Dengue virus proteins. The polypeptide may be a parasite protein that is expressed intracellularly, for example malaria proteins.

The polypeptide may be an active ingredient of a pharmaceutical composition, such as a vaccine or immunotherapy composition, optionally a candidate active ingredient for a new pharmaceutical composition. The term "active ingredient" as used herein refers to a polypeptide that is intended to induce an immune response and may include a polypeptide product of a vaccine or immunotherapy composition that is produced *in vivo* after administration to a subject. For a DNA or RNA immunotherapy composition, the polypeptide may be produced *in vivo* by the cells of a subject to whom the composition is administered. For a cell-based composition, the polypeptide may be processed and/or presented by cells of the composition, for example autologous dendritic cells or antigen presenting cells pulsed with the polypeptide or comprising an expression construct encoding the polypeptide. The pharmaceutical composition may comprise a polynucleoide or cell encoding one or more active ingredient polypeptides.

In other cases the polypeptide may be a target polypeptide antigen of a pharmaceutical, vaccine or immunotherapy composition. A polypeptide is a target polypeptide antigen if the composition is intended or designed to induce an immune response (e.g. a cytotoxic T cell response) that targets or is directed at the polypeptide. A target polypeptide antigen is typically a polypeptide that is expressed by a pathogenic organism, a virus or a diseased cell such as a cancer

cell. A target polypeptide antigens may be a TAA or a CTA. Presently, >200 clinical trials are investigating cancer vaccines with tumor antigens.

The polypeptide may be an allergen that enters the body of an individual through, for example, the skin, lung or oral routes.

Non-limiting examples of suitable polypeptides include those listed in one or more of Tables 2 to 6.

Genetic sequences may be obtained from the sequencing of biological materials. Sequencing can be done by any suitable method that determines DNA and/or RNA and/or amino acid sequences. The disclosure utilizes both the HLA genotypes and amino acid sequences. However, methods to identify HLA genotype from genetic sequences of an individual and methods of obtaining amino acid sequences derived from DNA or RNA sequence data are not the subject of the disclosure.

Table 2 - LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS. CTAs = **bold** and *

		5T4	Q13641.1	A1BG	P04217.1	A33	Q99795.1
A4GALT	Q9NPC4.1	AACT	P01011.1	AAG	Q9M6E9.1	ABI1	Q8IZP0.1
ABI2	Q9NYB9.1	ABL1	P00519.1	ABL-BCR	Q8WUG5.1	ABLIM3	O94929.1
ABLL	P42684.1	ABTB1	Q969K4.1	ACACA	Q13085.1	ACBD4	Q8NC06.1
ACO1	P21399.1	**ACRBP**	**Q8NEB7.1***	ACTL6A	O96019.1	**ACTL8**	**Q9H568.1***
ACTN4	O43707.1	ACVR1	Q04771.1	ACVR1B	P36896.1	ACVR2B	Q13705.1
ACVRL1	P37023.1	ACS2B	Q68CK6.1	ACSL5	Q9ULC5.1	ADAM-15	Q13444.1
ADAM17	P78536.1	**ADAM2**	**Q99965.1***	**ADAM29**	**Q9UKF5.1***	ADAM7	Q9H2U9.1
ADAP1	O75689.1	ADFP	Q99541.1	ADGRA3	Q8IWK6.1	ADGRF1	Q5T601.1
ADGRF2	Q8IZF7.1	ADGRL2	O95490.1	ADHFE1	Q8IWW8.1	AEN	Q8WTP8.1
AFF1	P51825.1	AFF4	Q9UHB7.1	AFP	P02771.1	AGAP2	Q99490.1
AGO1	Q9UL18.1	AGO3	Q9H9G7.1	AGO4	Q9HCK5.1	AGR2	O95994.1
AIFM2	Q9BRQ8.1	AIM2	O14862.1	AKAP-13	Q12802.1	**AKAP-3**	**O75969.1***
AKAP-4	**Q5JQC9.1***	AKIP1	Q9NQ31.1	AKT1	P31749.1	AKT2	P31751.1
AKT3	Q9Y243.1	ALDH1A1	P00352.1	ALK	Q9UM73.1	ALKBH1	Q13686.1
ALPK1	Q96QP1.1	AMIGO2	Q86SJ2.1	ANG2	O15123.1	**ANKRD45**	**Q5TZF3.1***
ANO1	Q5XXA6.1	ANP32A	P39687.1	ANXA2	P07355.1	APC	P25054.1
APEH	P13798.1	APOA2	P02652.1	APOD	P05090.1	APOL1	O14791.1
AR	P10275.1	ARAF	P10398.1	ARF4L	P49703.1	ARHGEF5	Q12774.1
ARID3A	Q99856.1	ARID4A	P29374.1	ARL6IP5	O75915.1	**ARMC3**	**B4DXS3.1***
ARMC8	Q8IUR7.1	ARTC1	P52961.1	**ARX**	**Q96QS3.1***	ATAD2	Q6PL18.1
ATIC	P31939.1	AURKC	Q9UQB9.1	AXIN1	O15169.1	AXL	P30530.1
BAAT	Q14032.1	BAFF	Q9Y275.1	**BAGE-1**	**Q13072.1***	**BAGE-2**	**Q86Y30.1***
BAGE-3	**Q86Y29.1***	**BAGE-4**	**Q86Y28.1**	**BAGE-5**	**Q86Y27.1***	BAI1	O14514.1
BAL	P19835.1	BALF2	P03227.1	BALF4	P03188.1	BALF5	P03198.1
BARF1	P03228.1	BBRF1	P03213.1	BCAN	Q96GW7.1	BCAP31	P51572.1
BCL-2	P10415.1	BCL2L1	Q07817.1	BCL6	P41182.1	BCL9	O00512.1
BCR	P11274.1	BCRF1	P03180.1	BDLF3	P03224.1	BGLF4	P13288.1
BHLF1	P03181.1	BHRF1	P03182.1	BILF1	P03208.1	BILF2	P03218.1
BIN1	O00499.1	BING-4	O15213.1	BIRC7	Q96CA5.1	BLLF1	P03200.1
BLLF2	P03199.1	BMI1	P35226.1	BMLF1	Q04360.1	BMPR1B	O00238.1
BMRF1	P03191.1	BNLF2a	P0C739.1	BNLF2b	Q8AZJ3.1	BNRF1	P03179.1
BRAF1	P15056.1	BRD4	O60885.1	**BRDT**	**Q58F21.1***	BRI3BP	Q8WY22.1

BRINP1 O60477.1	BRLF1 P03209.1	BTBD2 Q9BX70.1	BUB1B O60566.1
BVRF2 P03234.1	BXLF1 P03177.1	BZLF1 P03206.1	**C15orf60 Q7Z4M0.1***
CA 12-5 Q8WXI7.1	CA 19-9 Q969X2.1	CA195 Q5TG92.1	CA9 Q16790.1
CABYR O75952.1*	CADM4 Q8NFZ8.1	**CAGE1 Q8CT20.1***	CALCA P01258.1
CALR3 Q96L12.1	CAN P35658.1	CASC3 O15234.1	**CASC5 Q8NG31.1***
CASP5 P51878.1	CASP8 Q14790.1	CBFA2T2 O43439.1	CBFA2T3 O75081.1
CBL P22681.1	CBLB Q13191.1	CC3 Q9BUP3.1	**CCDC110 Q8TBZ0.1***
CCDC33 Q8N5R6.1*	**CCDC36 Q8IYA8.1***	CCDC6 Q16204.1	**CCDC62 Q6P9F0.1***
CCDC68 Q9H2F9.1	**CCDC83 Q8IWF9.1***	CCL13 Q99616.1	CCL2 P13500.1
CCL7 P80098.1	**CCNA1 P78396.1***	CCNA2 P20248.1	CCNB1 P14635.1
CCND1 P24385.1	CCNE2 O96020.1	CCNI Q14094.1	CCNL1 Q9UK58.1
CCR2 P41597.1	CD105 P17813.1	CD123 P26951.1	CD13 P15144.1
CD133 O43490.1	CD137 Q07011.1	CD138 P18827.1	CD157 Q10588.1
CD16A P08637.1	CD178 P48023.1	CD19 P15391.1	CD194 P51679.1
CD2 P06729.1	CD20 P11836.1	CD21 P20023.1	CD22 P20273.1
CD229 Q9HBG7.1	CD23 P06734.1	CD27 P26842.1	CD28 P10747.1
CD30 P28908.1	CD317 Q10589.1	CD33 P20138.1	CD350 Q9ULW2.1
CD36 P16671.1	CD37 P11049.1	CD4 P01730.1	CD40 P25942.1
CD40L P29965.1	CD45 P08575.1	CD47 Q08722.1	CD51 P06756.1
CD52 P31358.1	CD55 P08174.1	CD61 P05106.1	CD70 P32970.1
CD74 P08922.1	CD75 P15907.1	CD79B P40259.1	CD80 P33681.1
CD86 P42081.1	CD8a P01732.1	CD8b P10966.1	CD95 P25445.1
CD98 P08195.1	CDC123 O75794.1	CDC2 P06493.1	CDC27 P30260.1
CDC73 Q6P1J9.1	**CDCA1 Q9BZD4.1***	CDCP1 Q9H5V8.1	CDH3 P22223.1
CDK2AP1 O14519.1	CDK4 P11802.1	CDK7 P50613.1	CDKN1A P38936.1
CDKN2A P42771.1	CEA P06731.1	CEACAM1 Q86UE4.1	CENPK Q9BS16.1
CEP162 Q5TB80.1	**CEP290 O15078.1***	**CEP55 Q53EZ4.1***	CFL1 P23528.1
CH3L2 Q15782.1	CHEK1 O14757.1	CK2 P19784.1	CLCA2 Q9UQC9.1
CLOCK O15516.1	CLPP Q16740.1	CMC4 P56277.1	CML66 Q96RS6.1
CO-029 P19075.1	COTL1 Q14019.1	COX2 P35354.1	**COX6B2 Q6YFQ2.1***
CPSF1 Q10570.1	**CPXCR1 Q8N123.1***	CREBL2 O60519.1	CREG1 O75629.1
Cripto P13385.1	**CRISP2 P16562.1***	*CRK P46108.1	CRKL P46109.1
CRLF2 Q9HC73.1	CSAGE Q6PB30.1	**CT45 Q5HYN5.1***	**CT45A2 Q5DJT8.1***
CT45A3 Q8NHU0.1*	**CT45A4 Q8N7B7.1***	**CT45A5 Q6NSH3.1***	**CT45A6 P0DMU7.1***
CT46 Q86X24.1*	**CT47 Q5JQC4.1***	**CT47B1 P0C2P7.1***	**CTAGE2 Q96RT6.1***
cTAGE5 O15320.1*	**CTCFL Q8NI51.1***	CTDSP2 O14595.1	CTGF P29279.1
CTLA4 P16410.1	**CTNNA2 P26232.1***	CTNNB1 P35222.1	CTNND1 O60716.1
CTSH P09668.1	**CTSP1 A0RZH4.1***	CTTN Q14247.1	CXCR4 P61073.1
CXorf48 Q8WUE5.1*	**CXorf61 Q5H943.1***	Cyclin-E P24864.1	CYP1B1 Q16678.1
CypB P23284.1	CYR61 O00622.1	CS1 P28290.1	**CSAG1 Q6PB30.1***
CSDE1 O75534.1	CSF1 P09603.1	CSF1R P07333.1	CSF3R Q99062.1
CSK P41240.1	CSK23 Q8NEV1.1	DAPK3 O43293.1	DAZ1 Q9NQZ3.1
DBPC Q9Y2T7.1	**DCAF12 Q5T6F0.1***	DCT P40126.1	DCUN1D1 Q96GG9.1
DCUN1D3 Q8IWE4.1	DDR1 Q08345.1	DDX3X O00571.1	DDX6 P26196.1
DEDD O75618.1	DEK P35659.1	DENR O43583.1	DEPDC1 Q5TB30.1
DFNA5 O60443.1	DGAT2 Q96PD7.1	DHFR P00374.1	DKK1 O94907.1
DKK3 Q9UBP4.1	**DKKL1 Q9UK85.1***	DLEU1 O43261.1	DMBT1 Q9UGM3.1
DMRT1 Q9Y5R6.1*	**DNAJB8 Q8NHS0.1***	DNAJC8 O75937.1	DNMT3A Q9Y6K1.1
DPPA2 Q7Z7J5.1*	DR4 O00220.1	DR5 O14763.1	**DRG1 Q9Y295.1***
DSCR8 Q96T75.1	E2F3 O00716.1	E2F6 O75461.1	E2F8 A0AVK6.1
EBNA1 P03211.1	EBNA2 P12978.1	EBNA3 P12977.1	EBNA4 P03203.1
EBNA6 P03204.1	EBNA-LP Q8AZK7.1	E-cadherin P12830.1	ECT2 Q9H8V3.1
ECTL2 Q008S8.1	**EDAG Q9BXL5.1***	EEF2 P13639.1	EFNA1 P20827.1
EFS O43281.1	EFTUD2 Q15029.1	EGFL7 Q9UHF1.1	EGFR p00533.1
EI24 O14681.1	EIF4EBP1 Q13541.1	ELF3 P78545.1	ELF4 Q99607.1
ELOVL4 Q9GZR5.1*	EMP1 P54849.1	ENAH Q8N8S7.1	Endosialin Q9HCU0.1
ENO1 P06733.1	ENO2 P09104.1	ENO3 P13929.1	ENTPD5 O75356.1
EpCAM P16422.1	EPHA2 P29317.1	EPHA3 P29320.1	EPHB2 P29323.1
EPHB4 P54760.1	EPHB6 O15197.1	EPS8 Q12929.1	ERBB3 P21860.1
ERBB4 Q15303.1	EREG O14944.1	ERG P11308.1	ERVK-18 O42043.1
ERVK-19 O71037.1	ESR1 P03372.1	ETAA1 Q9NY74.1	ETS1 P14921.1

ETS2 P15036.1	ETV1 P50549.1	ETV5 P41161.1	ETV6 P41212.1
EVI5 O60447.1	EWSR1 Q01844.1	EYA2 O00167.1	EZH2 Q15910.1
FABP7 O15540.1	**FAM133A Q8N9E0.1***	FAM13A O94988.1	**FAM46D Q8NEK8.1***
FAM58BP P0C7Q3.1	FANCG O15287.1	**FATE1 Q969F0.1***	**FBXO39 Q8N4B4.1***
FBXW11 Q9UKB1.1	FCHSD2 O94868.1	FER P16591.1	FES P07332.1
FEV Q99581.1	FGF10 O15520.1	FGF23 Q9GZV9.1	FGF3 P11487.1
FGF4 P08620.1	FGF5 P12034.1	FGFR1 P11362.1	FGFR2 P21802.1
FGFR3 P22607.1	FGFR4 P22455.1	FGR P09769.1	FLI1 Q01543.1
FLT3 P36888.1	FMNL1 O95466.1	FMOD Q06828.1	**FMR1NB Q8N0W7.1***
FN1 P02751.1	Fn14 Q9NP84.1	FNIP2 Q9P278.1	FOLR1 P15328.1
FOS P01100.1	FosB P53539.1	FOSL1 P15407.1	FOXM1 Q08050.1
FOXO1 Q12778.1	FOXO3 O43524.1	FRAT1 Q92837.1	FRMD3 A2A2Y4.1
FSIP1 Q8NA03.1	FSIP2 Q5CZC0.1	FSTL3 O95633.1	**FTHL17 Q9BXU8.1***
FUNDC2 Q9BWH2.1	FUS P35637.1	FUT1 P19526.1	FUT3 P21217.1
FYN P06241.1	GAB2 Q9UQC2.1	GADD45G O95257.1	**GAGE-1 Q13065.1**
GAGE12B/C/D/E A1L429.1	**GAGE12F P0CL80.1**	**GAGE12G P0CL81.1**	**GAGE12H A6NDE8.1**
GAGE12I P0CL82.1	**GAGE12J A6NER3.1**	**GAGE-2 Q6NT46.1**	**GAGE-3 Q13067.1**
GAGE-4 Q13068.1	**GAGE-5 Q13069.1**	**GAGE-6 Q13070.1**	**GAGE-7 O76087.1**
GAGE-8 Q9UEU5.1	GALGT2 Q00973.1	GAS7 O60861.1	GASZ Q8WWH4.1
GATA-3 P23771.1	GBU4-5 Q587J7.1	GCDFP-15 P12273.1	GFAP P14136.1
GFI1 Q99684.1	Ghrelin Q9UBU3.1	GHSR Q92847.1	GIPC1 O14908.1
GITR Q9Y5U5.1	GKAP1 Q5VSY0.1	GLI1 P08151.1	Glypican-3 P51654.1
GML Q99445.1	GNA11 P29992.1	GNAQ P50148.1	GNB2L1 P63244.1
GOLGA5 Q8TBA6.1	gp100 P40967.1	gp75 P17643.1	Gp96 P14625.1
GPAT2 Q6NUI2.1*	**GPATCH2 Q9NW75.1***	GPC-3 P51654.1	GPNMB Q14956.1
GPR143 P51810.1	GPR89A B7ZAQ6.1	GRB2 P62993.1	GRP78 P11021.1
GUCY1A3 Q02108.1	H3F3A P84243.1	**HAGE Q9NXZ2.1***	hANP P01160.1
HBEGF Q99075.1	hCG-beta P01233.1	HDAC1 Q13547.1	HDAC2 Q92769.1
HDAC3 O15379.1	HDAC4 P56524.1	HDAC5 Q9UQL6.1	HDAC6 Q9UBN7.1
HDAC7 Q8WUI4.1	HDAC8 Q9BY41.1	HDAC9 Q9UKV0.1	HEATR1 Q9H583.1
Hepsin P05981.1	Her2/neu P04626.1	HERC2 O95714.1	HERV-K104 P61576.1
HEXB P07686.1	HEXIM1 O94992.1	HGRG8 Q9Y5A9.1	HIPK2 Q9H2X6.1
HJURP Q8NCD3.1	HMGB1 P09429.1	HMOX1 P09601.1	HNRPL P14866.1
HOM-TES-85 Q9P127.1*	**HORMAD1 Q86X24.1***	**HORMAD2 Q8N7B1.1***	HPSE Q9Y251.1
HPV16 E6 P03126.1	HPV16 E7 P03129.1	HPV18 E6 P06463.1	HPV18 E7 P06788.1
HRAS P01112.1	HSD17B13 Q7Z5P4.1	HSP105 Q92598.1	HSP60 P10809.1
HSPA1A P08107.1	**HSPB9 Q9BQS6.1***	HST-2 P10767.1	HT001 Q2TB18.1
hTERT O14746.1	HUS1 O60921.1	ICAM-1 P05362.1	IDH1 O75874.1
IDO1 P14902.1	IER3 P46695.1	IGF1R P08069.1	**IGFS11 Q5DX21.1***
IL13RA2 Q14627.1*	**IMP-3 Q9NV31.1***	ING3 Q9NXR8.1	INPPL1 O15357.1
INTS6 Q9UL03.1	IRF4 Q15306.1	IRS4 O14654.1	ITGA5 P08648.1
ITGB8 P26012.1	ITPA Q9BY32.1	ITPR2 Q14571.1	JAK2 O60674.1
JAK3 P52333.1	**JARID1B Q9UGL1.1***	JAZF1 Q86VZ6.1	JNK1 P45983.1
JNK2 P45984.1	JNK3 P53779.1	JTB O76095.1	JUN P05412.1
JUP P14923.1	K19 P08727.1	KAAG1 Q9UBP8.1	Kallikrein 14 Q9P0G3.1
Kallikrein 4 Q9Y5K2.1	KAT6A Q92794.1	KDM1A O60341.1	KDM5A P29375.1
KIAA0100 Q14667.1*	KIAA0336 Q8IWJ2.1	KIAA1199 Q8WUJ3.1	KIAA1641 A6QL64.1
KIF11 P52732.1	KIF1B O60333.1	KIF20A O95235.1	KIT P10721.1
KLF4 O43474.1	KLHL41 O60662.1	KLK10 O43240.1	KMT2D O14686.1
KOC1 O00425.1	K-ras P01116.1	KRIT1 O00522.1	KW-12 P62913.1
KW-2 Q96RS0.1	KW-5 (SEBD4) Q9H0Z9.1	KW-7 O75475.1	L1CAM P32004.1
L53 Q96EL3.1	L6 Q9BTT4.1	LAG3 P18627.1	**Lage-1 O75638.1***
LATS1 O95835.1	LATS2 Q9NRM7.1	LCMT2 O60294.1	LCP1 P13796.1
LDHC P07864.1*	LDLR P01130.1	**LEMD1 Q68G75.1***	Lengsin Q5TDP6.1
LETMD1 Q6P1Q0.1	LGALS3BP Q08380.1	LGALS8 O00214.1	LIN7A O14910.1
LIPI Q6XZB0.1*	LIV-1 Q13433.1	LLGL1 Q15334.1	LMO1 P25800.1
LMO2 P25791.1	LMP1 P03230.1	LMP2 P13285.1	**LOC647107 Q8TAI5.1***
LOXL2 Q9Y4K0.1	LRP1 Q07954.1	LRRN2 O75325.1	LTF P02788.1
LTK P29376.1	LZTS1 Q9Y250.1	**LY6K Q17RY6.1***	LYN P07948.1

LYPD6B Q8NI32.1*	MAEA Q7L5Y9.1	**MAEL Q96JY0.1***	MAF O75444.1
MAFF Q9ULX9.1	MAFG O15525.1	MAFK O60675.1	**MAGE-A1 P43355.1***
MAGE-A10 P43363.1*	**MAGE-A11 P43364.1***	**MAGE-A12 P43365.1***	**MAGE-A2 P43356.1***
MAGE-A2B Q6P448.1*	**MAGE-A3 P43357.1***	**MAGE-A4 P43358.1***	**MAGE-A5 P43359.1***
MAGE-A6 P43360.1*	**MAGE-A8 P43361.1***	**MAGE-A9 P43362.1***	**MAGE-B1 P43366.1***
MAGE-B2 O15479.1*	**MAGE-B3 O15480.1***	**MAGE-B4 O15481.1***	**MAGE-B5 Q9BZ81.1***
MAGE-B6 Q8N7X4.1*	**MAGE-C1 O60732.1***	**MAGE-C2 Q9UBF1.1***	**MAGE-C3 Q8TD91.1***
mammaglobin-A Q13296.1	MANF P55145.1	MAP2K2 P36507.1	MAP2K7 O14733.1
MAP3K7 O43318.1	MAP4K5 Q9Y4K4.1	MART1 Q16655.1	MART-2 Q5VTY9.1
MAS1 P04201.1	MC1R Q01726.1	**MCAK Q99661.1***	MCF2 P10911.1
MCF2L O15068.1	MCL1 Q07820.1	MCTS1 Q9ULC4.1	MCSP Q6UVK1.1
MDK P21741.1	MDM2 Q00987.1	MDM4 O15151.1	ME1 P48163.1
ME491 P08962.1	MECOM Q03112.1	MELK Q14680.1	MEN1 O00255.1
MERTK Q12866.1	MET P08581.1	MFGE8 Q08431.1	MFHAS1 Q9Y4C4.1
MFI2 P08582.1	MGAT5 Q09328.1	Midkine P21741.1	MIF P14174.1
MKI67 P46013.1	MLH1 P40692.1	MLL Q03164.1	MLLT1 Q03111.1
MLLT10 P55197.1	MLLT11 Q13015.1	MLLT3 P42568.1	MLLT4 P55196.1
MLLT6 P55198.1	MMP14 P50281.1	MMP2 P08253.1	MMP7 P09237.1
MMP9 P14780.1	MOB3B Q86TA1.1	**MORC1 Q86VD1.1***	**MPHOSPH1 Q96Q89.1***
MPL P40238.1	MRAS O14807.1	MRP1 P33527.1	MRP3 O15438.1
MRPL28 Q13084.1	MRPL30 Q8TCC3.1	MRPS11 P82912.1	MSLN Q13421.1
MTA1 Q13330.1	MTA2 O94776.1	MTA3 Q9BTC8.1	MTCP1 P56278.1
MTSS1 O43312.1	MUC-1 P15941.1	MUC-2 Q02817.1	MUC-3 Q02505.1
MUC-4 Q99102.1	MUC-5AC P98088.1	MUC-6 Q6W4X9.1	MUM1 Q2TAK8.1
MUM2 Q9Y5R8.1	MYB P10242.1	MYC P01106.1	MYCL P12524.1
MYCLP1 P12525.1	MYCN P04198.1	MYD88 Q99836.1	MYEOV Q96EZ4.1
MYO1B O43795.1	**NA88-A P0C5K6.1***	NAE1 Q13564.1	Napsin-A O96009.1
NAT6 Q93015.1	NBAS A2RRP1.1	NBPF12 Q5TAG4.1	NCOA4 Q13772.1
NDC80 O14777.1	NDUFC2 O95298.1	Nectin-4 Q96NY8.1	NEK2 P51955.1
NEMF O60524.1	NENF Q9UMX5.1	NEURL1 O76050.1	NFIB O00712.1
NFKB2 Q00653.1	NF-X1 Q12986.1	NFYC Q13952.1	NGAL P80188.1
NGEP Q6IWH7.1	NKG2D-L1 Q9BZM6.1	NKG2D-L2 Q9BZM5.1	NKG2D-L3 Q9BZM4.1
NKG2D-L4 Q8TD07.1	NKX3.1 Q99801.1	NLGN4X Q8N0W4.1	**NLRP4 Q96MN2.1***
NNMT P40261.1	**NOL4 O94818.1***	NOTCH2 Q04721.1	NOTCH3 Q9UM47.1
NOTCH4 Q99466.1	NOV P48745.1	NPM1 P06748.1	**NR6A1 Q15406.1***
N-RAS P01111.1	NRCAM Q92823.1	NRP1 O14786.1	NSE1 Q96KN4.1
NSE2 Q96KN1.1	NTRK1 P04629.1	NUAK1 O60285.1	NUGGC Q68CJ6.1
NXF2 Q9GZY0.1*	**NXF2B Q5JRM6.1***	NY-BR-1 Q9BXX3.1	NYD-TSPG Q9BWV7.1
NY-ESO-1 P78358.1*	NY-MEL-1 P57729.1	OCA2 Q04671.1	**ODF1 Q14990.1***
ODF2 Q5BJF6.1*	**ODF3 Q96PU9.1***	**ODF4 Q2M2E3.1***	OGG1 O15527.1
OGT O15294.1	**OIP5 O43482.1***	OS9 Q13438.1	**OTOA Q05BM7.1***
OX40 P43489.1	OX40L P23510.1	P53 P04637.1	P56-LCK P06239.1
PA2G4 Q9UQ80.1	**PAGE1 O75459.1***	**PAGE2 Q7Z2X2.1***	**PAGE2B Q5JRK9.1***
PAGE3 Q5JUK9.1*	**PAGE4 O60829.1***	**PAGE5 Q96GU1.1***	PAK2 Q13177.1
PANO1 I0J062.1	PAP Q06141.1	PAPOLG Q9BWT3.1	PARK2 O60260.1
PARK7 Q99497.1	PARP12 Q9H0J9.1	**PASD1 Q8IV76.1***	PAX3 P23760.1
PAX5 Q02548.1	PBF P00751.1	**PBK Q96KB5.1***	PBX1 P40424.1
PCDC1 Q15116.1	PCM1 Q15154.1	PCNXL2 A6NKB5.1	PDGFB P01127.1
PDGFRA P16234.1	**PEPP2 Q9HAU0.1***	PGF P49763.1	PGK1 P00558.1
PHLDA3 Q9Y5J5.1	PHLPP1 O60346.1	PIAS1 O75925.1	PIAS2 O75928.1
PIK3CA P42336.1	PIK3CD O00329.1	PIK3R2 O00459.1	PIM1 P11309.1
PIM2 Q9P1W9.1	PIM3 Q86V86.1	PIR O00625.1	**PIWIL1 Q96J94.1***
PIWIL2 Q8TC59.1*	PIWIL3 Q7Z3Z3.1	PIWIL4 Q7Z3Z4.1	PKN3 Q6P5Z2.1
PLA2G16 P53816.1	**PLAC1 Q9HBJ0.1***	PLAG1 Q6DJT9.1	PLEKHG5 O94827.1
PLK3 Q9H4B4.1	PLS3 P13797.1	PLVAP Q9BX97.1	PLXNB1 O43157.1
PLXNB2 O15031.1	PML P29590.1	PML-RARA Q96QH2.1	**POTEA Q6S8J7.1***
POTEB Q6S5H4.1*	**POTEC B2RU33.1***	**POTED Q86YR6.1***	**POTEE Q6S8J3.1***
POTEG Q6S5H5.1*	**POTEH Q6S545.1***	PP2A P63151.1	PPAPDC1B Q8NEB5.1
PPFIA1 Q13136.1	PPIG Q13427.1	PPP2R1B P30154.1	**PRAME P78395.1***
PRDX5 P30044.1	PRKAA1 Q13131.1	PRKCI P41743.1	**PRM1 P04553.1***

PRM2 P04554.1*	PRMT3 O60678.1	PRMT6 Q96LA8.1	PDL1 Q9NZQ7.1
PROM1 O43490.1	**PRSS54 Q6PEW0.1***	**PRSS55 Q6UWB4.1***	PRTN3 P24158.1
PRUNE Q86TP1.1	PRUNE2 Q8WUY3.1	PSA P07288.1	PSCA D3DWI6.1
PSMA Q04609.1	PSMD10 O75832.1	PSGR Q9H255.1	PSP-94 Q1L6U9.1
PTEN P60484.1	PTH-rP P12272.1	PTK6 Q13882.1	**PTPN20A Q4JDL3.1***
PTPRK Q15262.1	PTPRZ P23471.1	PTTG-1 O95997.1	PTTG2 Q9NZH5.1
PTTG3 Q9NZH4.1	PXDNL A1KZ92.1	RAB11FIP3 O75154.1	RAB8A P61006.1
RAD1 O60671.1	RAD17 O75943.1	RAD51C O43502.1	RAF1 P04049.1
RAGE-1 Q9UQ07.1	RAP1A P62834.1	RARA P10276.1	RASSF10 A6NK89.1
RB1 P06400.1	RBL2 Q08999.1	**RBM46 Q8TBY0.1***	RBP4 P02753.1
RCAS1 O00559.1	RCVRN P35243.1	RECQL4 O94761.1	RET P07949.1
RGS22 Q8NE09.1*	RGS5 O15539.1	RHAMM O75330.1	RhoC P08134.1
RHOXF2 Q9BQY4.1	RL31 P62888.1	RNASET2 O00584.1	RNF43 Q68DV7.1
RNF8 O76064.1	RON Q04912.1	**ROPN1A Q9HAT0.1***	ROR1 Q01973.1
RPA1 O95602.1	RPL10A P62906.1	RPL7A P62424.1	RPS2 P15880.1
RPS6KA5 O75582.1	RPSA P08865.1	**RQCD1 Q92600.1***	RRAS2 P62070.1
RSL1D1 O76021.1	RTKN Q9BST9.1	RUNX1 Q01196.1	RUNX2 Q13950.1
RYK P34925.1	**SAGE1 Q9NXZ1.1***	SART2 Q9UL01.1	SART3 Q15020.1
SASH1 O94885.1	sCLU P10909.1	SCRN1 Q12765.1	SDCBP O00560.1
SDF-1 P48061.1	SDHD O14521.1	SEC31A O94979.1	SEC63 Q9UGP8.1
Semaphorin 4D Q92854.1	**SEMG1 P04279.1***	SFN P31947.1	SH2B2 O14492.1
SH2D1B O14796.1	SH3BP1 Q9Y3L3.1	SHB Q15464.1	SHC3 Q92529.1
SIRT2 Q8IXJ6.1	SIVA1 O15304.1	SKI P12755.1	SLBP A9UHW6.1
SLC22A10 Q63ZE4.1	SLC25A47 Q6Q0C1.1	SLC35A4 Q96G79.1	SLC45A3 Q96JT2.1
SLC4A1AP Q9BWU0.1	**SLCO6A1 Q86UG4.1***	SLITRK6 Q9H5Y7.1	Sm23 P27701.1
SMAD5 Q99717.1	SMAD6 O43541.1	SMO Q99835.1	Smt3B P61956.1
SNRPD1 P62314.1	SOS1 Q07889.1	SOX-2 P48431.1	SOX-6 P35712.1
SOX-11 P35716 .1	**SPA17 Q15506.1***	**SPACA3 Q8IXA5.1***	**SPAG1 Q07617.1***
SPAG17 Q6Q759.1*	**SPAG4 Q9NPE6.1***	**SPAG6 O75602.1***	**SPAG8 Q99932.1***
SPAG9 O60271.1*	**SPANXA1 Q9NS26.1***	**SPANXB Q9NS25.1***	**SPANXC Q9NY87.1***
SPANXD Q9BXN6.1*	**SPANXE Q8TAD1.1***	**SPANXN1 Q5VSR9.1***	**SPANXN2 Q5MJ10.1***
SPANXN3 Q5MJ09.1*	**SPANXN4 Q5MJ08.1***	**SPANXN5 Q5MJ07.1***	**SPATA19 Q7Z5L4.1***
SPEF2 Q9C093.1*	SPI1 P17947.1	**SPINLW1 O95925.1***	**SPO11 Q9Y5K1.1***
SRC P12931.1	SSPN Q14714.1	**SSX-1 Q16384.1***	**SSX-2 Q16385.1***
SSX-3 Q99909.1*	**SSX-4 O60224.1***	**SSX-5 O60225.1***	**SSX-6 Q7RTT6.1***
SSX-7 Q7RTT5.1*	**SSX-9 Q7RTT3.1***	ST18 O60284.1	STAT1 P42224.1
STEAP1 Q9UHE8.1	STK11 Q15831.1	STK25 O00506.1	STK3 Q13188.1
STN Q9H668.1	SUPT7L O94864.1	Survivin O15392.1	SUV39H1 O43463.1
SYCE1 Q8N0S2.1	**SYCP1 Q15431.1**	SYCP3 Q8IZU3.1	SYT Q15532.1
TA-4 Q96RI8.1	TACC1 O75410.1	TAF1B Q53T94.1	TAF4 O00268.1
TAF7L Q5H9L4.1*	**TAG-1 Q02246.1***	TAL1 P17542.1	TAL2 Q16559.1
TAPBP O15533.1	TATI P00995.1	TAX1BP3 O14907.1	TBC1D3 Q8IZP1.1
TBP-1 P17980.1	TCL1A P56279.1	TCL1B O95988.1	TDHP Q9BT92.1
TDRD1 Q9BXT4.1*	**TDRD4 Q9BXT8.1***	**TDRD6 O60522.1***	**TEKT5 Q96M29.1***
TEX101 Q9BY14.1*	**TEX14 Q8IWB6.1***	**TEX15 Q9BXT5.1***	**TEX38 Q6PEX7.1***
TF P02787.1	**TFDP3 Q5H9I0.1***	TFE3 P19532.1	TGFBR1 P36897.1
TGFBR2 P37173.1	**THEG Q9P2T0.1***	TIE2 Q02763.1	TIPRL O75663.1
TLR2 O60603.1	**TMEFF1 Q8IYR6.1***	**TMEFF2 Q9UIK5.1***	**TMEM108 Q6UXF1.1***
TMEM127 O75204.1	**TMPRSS12 Q86WS5.1***	TNC P24821.1	TNFRSF17 Q02223.1
TNFSF15 O95150.1	TNK2 Q07912.1	TOMM34 Q15785.1	TOP2A P11388.1
TOP2B Q02880.1	TOR3A Q9H497.1	TP73 O15350.1	TPA1 8N543.1
TPGS2 Q68CL5.1	TPI1 P60174.1	TPL2 P41279.1	TPM4 P67936.1
TPO P40225.1	**TPPP2 P59282.1***	TPR P12270.1	**TPTE P56180.1***
TRAF5 O00463.1	**TRAG-3 Q9Y5P2.1***	TRGC2 P03986.1	TRIM24 O15164.1
TRIM37 O94972.1	TRIM68 Q6AZZ1.1	TRPM8 Q7Z2W7.1	**TSGA10 Q9BZW7.1***
TSP50 Q9UI38.1*	TSPAN6 O43657.1	**TSPY1 Q01534.1***	**TSPY2 A6NKD2.1***
TSPY3 Q6B019.1*	TSPYL1 Q9H0U9.1	**TSSK6 Q9BXA6.1***	TTC23 Q5W5X9.1
TTK P33981.1*	**TULP2 O00295.1***	TUSC2 O75896.1	TWEAK O43508.1
TXNIP Q9H3M7.1	TYMS P04818.1	TYR P14679.1	U2 snRNP B P08579.1
U2AF1 Q01081.1	UBD O15205.1	UBE2A P49459.1	UBE2C O00762.1

UBE2V1 Q13404.1	UBE4B O95155.1	UBR5 O95071.1	UBXD5 Q5T124.1
UFL1 O94874.1	URI1 O94763.1	URLC10 Q17RY6.1	UROC1 Q96N76.1
USP2 O75604.1	USP4 Q13107.1	VAV1 P15498.1	VCX3A Q9NNX9.1
VEGFR1 P17948.1	VEGFR2 P35968.1	VHL P40337.1	VIM P08670.1
VWA5A O00534.1	WHSC2 Q9H3P2.1	WISP1 O95388.1	WNK2 Q9Y3S1.1
WNT10B O00744.1	WNT3 P56703.1	WNT-5a P41221.1	WT1 P19544.1
WWP1 Q9H0M0.1	**XAGE-1 Q9HD64.1***	**XAGE-2 Q96GT9.1***	**XAGE-3 Q8WTP9.1***
XAGE-4 Q8WWM0.1	**XAGE-5 Q8WWM1.1***	XBP1 P17861.1	XPO1 O14980.1
XRCC3 O43542.1	YB-1 P67809.1	YEATS4 O95619.1	YES1 P07947.1
YKL-40 P36222.1	ZBTB7A O95365.1	ZBTB7C A1YPR0.1	ZEB1 P37275.1
ZFYVE19 Q96K21.1	**ZNF165 P49910.1***	ZNF185 O15231.1	ZNF217 O75362.1
ZNF320 A2RRD8.1	ZNF395 Q9H8N7.1	**ZNF645 Q8N7E2.1***	ZUBR1 Q5T4S7.1
ZW10 O43264.1	ZWINT O95229.1		

Table 2 - LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS CTAs = **bold** and *

	5T4 Q13641.1	A1BG P04217.1	A33 Q99795.1
A4GALT Q9NPC4.1	AACT P01011.1	AAG Q9M6E9.1	ABI1 Q8IZP0.1
ABI2 Q9NYB9.1	ABL1 P00519.1	ABL-BCR Q8WUG5.1	ABLIM3 O94929.1
ABLL P42684.1	ABTB1 Q969K4.1	ACACA Q13085.1	ACBD4 Q8NC06.1
ACO1 P21399.1	ACRBP Q8NEB7.1	ACTL6A O96019.1	ACTL8 Q9H568.1
ACTN4 O43707.1	ACVR1 Q04771.1	ACVR1B P36896.1	ACVR2B Q13705.1
ACVRL1 P37023.1	ACS2B Q68CK6.1	ACSL5 Q9ULC5.1	ADAM-15 Q13444.1
ADAM17 P78536.1	ADAM2 Q99965.1	ADAM29 Q9UKF5.1	ADAM7 Q9H2U9.1
ADAP1 O75689.1	ADFP Q99541.1	ADGRA3 Q8IWK6.1	ADGRF1 Q5T601.1
ADGRF2 Q8IZF7.1	ADGRL2 O95490.1	ADHFE1 Q8IWW8.1	AEN Q8WTP8.1
AFF1 P51825.1	AFF4 Q9UHB7.1	AFP P02771.1	AGAP2 Q99490.1
AGO1 Q9UL18.1	AGO3 Q9H9G7.1	AGO4 Q9HCK5.1	AGR2 O95994.1
AIFM2 Q9BRQ8.1	AIM2 O14862.1	AKAP-13 Q12802.1	AKAP-3 O75969.1
AKAP-4 Q5JQC9.1	AKIP1 Q9NQ31.1	AKT1 P31749.1	AKT2 P31751.1
AKT3 Q9Y243.1	ALDH1A1 P00352.1	ALK Q9UM73.1	ALKBH1 Q13686.1
ALPK1 Q96QP1.1	AMIGO2 Q86SJ2.1	ANG2 O15123.1	ANKRD45 Q5TZF3.1
ANO1 Q5XXA6.1	ANP32A P39687.1	ANXA2 P07355.1	APC P25054.1
APEH P13798.1	APOA2 P02652.1	APOD P05090.1	APOL1 O14791.1
AR P10275.1	ARAF P10398.1	ARF4L P49703.1	ARHGEF5 Q12774.1
ARID3A Q99856.1	ARID4A P29374.1	ARL6IP5 O75915.1	ARMC3 B4DXS3.1
ARMC8 Q8IUR7.1	ARTC1 P52961.1	ARX Q96QS3.1	ATAD2 Q6PL18.1
ATIC P31939.1	AURKC Q9UQB9.1	AXIN1 O15169.1	AXL P30530.1
BAAT Q14032.1	BAFF Q9Y275.1	BAGE-1 Q13072.1	BAGE-2 Q86Y30.1
BAGE-3 Q86Y29.1	BAGE-4 Q86Y28.1	BAGE-5 Q86Y27.1	BAI1 O14514.1
BAL P19835.1	BALF2 P03227.1	BALF4 P03188.1	BALF5 P03198.1
BARF1 P03228.1	BBRF1 P03213.1	BCAN Q96GW7.1	BCAP31 P51572.1
BCL-2 P10415.1	BCL2L1 Q07817.1	BCL6 P41182.1	BCL9 O00512.1
BCR P11274.1	BCRF1 P03180.1	BDLF3 P03224.1	BGLF4 P13288.1
BHLF1 P03181.1	BHRF1 P03182.1	BILF1 P03208.1	BILF2 P03218.1
BIN1 O00499.1	BING-4 O15213.1	BIRC7 Q96CA5.1	BLLF1 P03200.1
BLLF2 P03199.1	BMI1 P35226.1	BMLF1 Q04360.1	BMPR1B O00238.1
BMRF1 P03191.1	BNLF2a P0C739.1	BNLF2b Q8AZJ3.1	BNRF1 P03179.1
BRAF1 P15056.1	BRD4 O60885.1	BRDT Q58F21.1	BRI3BP Q8WY22.1
BRINP1 O60477.1	BRLF1 P03209.1	BTBD2 Q9BX70.1	BUB1B O60566.1
BVRF2 P03234.1	BXLF1 P03177.1	BZLF1 P03206.1	C15orf60 Q7Z4M0.1
CA 12-5 Q8WXI7.1	CA 19-9 Q969X2.1	CA195 Q5TG92.1	CA9 Q16790.1
CABYR O75952.1	CADM4 Q8NFZ8.1	CAGE1 Q8CT20.1	CALCA P01258.1
CALR3 Q96L12.1	CAN P35658.1	CASC3 O15234.1	CASC5 Q8NG31.1
CASP5 P51878.1	CASP8 Q14790.1	CBFA2T2 O43439.1	CBFA2T3 O75081.1
CBL P22681.1	CBLB Q13191.1	CC3 Q9BUP3.1	CCDC110 Q8TBZ0.1
CCDC33 Q8N5R6.1	CCDC36 Q8IYA8.1	CCDC6 Q16204.1	CCDC62 Q6P9F0.1
CCDC68 Q9H2F9.1	CCDC83 Q8IWF9.1	CCL13 Q99616.1	CCL2 P13500.1
CCL7 P80098.1	CCNA1 P78396.1	CCNA2 P20248.1	CCNB1 P14635.1

CCND1 P24385.1	CCNE2 O96020.1	CCNI Q14094.1	CCNL1 Q9UK58.1
CCR2 P41597.1	CD105 P17813.1	CD123 P26951.1	CD13 P15144.1
CD133 O43490.1	CD137 Q07011.1	CD138 P18827.1	CD157 Q10588.1
CD16A P08637.1	CD178 P48023.1	CD19 P15391.1	CD194 P51679.1
CD2 P06729.1	CD20 P11836.1	CD21 P20023.1	CD22 P20273.1
CD229 Q9HBG7.1	CD23 P06734.1	CD27 P26842.1	CD28 P10747.1
CD30 P28908.1	CD317 Q10589.1	CD33 P20138.1	CD350 Q9ULW2.1
CD36 P16671.1	CD37 P11049.1	CD4 P01730.1	CD40 P25942.1
CD40L P29965.1	CD45 P08575.1	CD47 Q08722.1	CD51 P06756.1
CD52 P31358.1	CD55 P08174.1	CD61 P05106.1	CD70 P32970.1
CD74 P08922.1	CD75 P15907.1	CD79B P40259.1	CD80 P33681.1
CD86 P42081.1	CD8a P01732.1	CD8b P10966.1	CD95 P25445.1
CD98 P08195.1	CDC123 O75794.1	CDC2 P06493.1	CDC27 P30260.1
CDC73 Q6P1J9.1	CDCA1 Q9BZD4.1	CDCP1 Q9H5V8.1	CDH3 P22223.1
CDK2AP1 O14519.1	CDK4 P11802.1	CDK7 P50613.1	CDKN1A P38936.1
CDKN2A P42771.1	CEA P06731.1	CEACAM1 Q86UE4.1	CENPK Q9BS16.1
CEP162 Q5TB80.1	CEP290 O15078.1	CEP55 Q53EZ4.1	CFL1 P23528.1
CH3L2 Q15782.1	CHEK1 O14757.1	CK2 P19784.1	CLCA2 Q9UQC9.1
CLOCK O15516.1	CLPP Q16740.1	CMC4 P56277.1	CML66 Q96RS6.1
CO-029 P19075.1	COTL1 Q14019.1	COX2 P35354.1	COX6B2 Q6YFQ2.1
CPSF1 Q10570.1	CPXCR1 Q8N123.1	CREBL2 O60519.1	CREG1 O75629.1
Cripto P13385.1	CRISP2 P16562.1	CRK P46108.1	CRKL P46109.1
CRLF2 Q9HC73.1	CSAGE Q6PB30.1	CT45 Q5HYN5.1	CT45A2 Q5DJT8.1
CT45A3 Q8NHU0.1	CT45A4 Q8N7B7.1	CT45A5 Q6NSH3.1	CT45A6 P0DMU7.1
CT46 Q86X24.1	CT47 Q5JQC4.1	CT47B1 P0C2P7.1	CTAGE2 Q96RT6.1
cTAGE5 O15320.1	CTCFL Q8NI51.1	CTDSP2 O14595.1	CTGF P29279.1
CTLA4 P16410.1	CTNNA2 P26232.1	CTNNB1 P35222.1	CTNND1 O60716.1
CTSH P09668.1	CTSP1 A0RZH4.1	CTTN Q14247.1	CXCR4 P61073.1
CXorf48 Q8WUE5.1	CXorf61 Q5H943.1	Cyclin-E P24864.1	CYP1B1 Q16678.1
CypB P23284.1	CYR61 O00622.1	CS1 P28290.1	CSAG1 Q6PB30.1
CSDE1 O75534.1	CSF1 P09603.1	CSF1R P07333.1	CSF3R Q99062.1
CSK P41240.1	CSK23 Q8NEV1.1	DAPK3 O43293.1	DAZ1 Q9NQZ3.1
DBPC Q9Y2T7.1	DCAF12 Q5T6F0.1	DCT P40126.1	DCUN1D1 Q96GG9.1
DCUN1D3 Q8IWE4.1	DDR1 Q08345.1	DDX3X O00571.1	DDX6 P26196.1
DEDD O75618.1	DEK P35659.1	DENR O43583.1	DEPDC1 Q5TB30.1
DFNA5 O60443.1	DGAT2 Q96PD7.1	DHFR P00374.1	DKK1 O94907.1
DKK3 Q9UBP4.1	DKKL1 Q9UK85.1	DLEU1 O43261.1	DMBT1 Q9UGM3.1
DMRT1 Q9Y5R6.1	DNAJB8 Q8NHS0.1	DNAJC8 O75937.1	DNMT3A Q9Y6K1.1
DPPA2 Q7Z7J5.1	DR4 O00220.1	DR5 O14763.1	DRG1 Q9Y295.1
DSCR8 Q96T75.1	E2F3 O00716.1	E2F6 O75461.1	E2F8 A0AVK6.1
EBNA1 P03211.1	EBNA2 P12978.1	EBNA3 P12977.1	EBNA4 P03203.1
EBNA6 P03204.1	EBNA-LP Q8AZK7.1	E-cadherin P12830.1	ECT2 Q9H8V3.1
ECTL2 Q008S8.1	EDAG Q9BXL5.1	EEF2 P13639.1	EFNA1 P20827.1
EFS O43281.1	EFTUD2 Q15029.1	EGFL7 Q9UHF1.1	EGFR p00533.1
EI24 O14681.1	EIF4EBP1 Q13541.1	ELF3 P78545.1	ELF4 Q99607.1
ELOVL4 Q9GZR5.1	EMP1 P54849.1	ENAH Q8N8S7.1	Endosialin Q9HCU0.1
ENO1 P06733.1	ENO2 P09104.1	ENO3 P13929.1	ENTPD5 O75356.1
EpCAM P16422.1	EPHA2 P29317.1	EPHA3 P29320.1	EPHB2 P29323.1
EPHB4 P54760.1	EPHB6 O15197.1	EPS8 Q12929.1	ERBB3 P21860.1
ERBB4 Q15303.1	EREG O14944.1	ERG P11308.1	ERVK-18 O42043.1
ERVK-19 O71037.1	ESR1 P03372.1	ETAA1 Q9NY74.1	ETS1 P14921.1
ETS2 P15036.1	ETV1 P50549.1	ETV5 P41161.1	ETV6 P41212.1
EVI5 O60447.1	EWSR1 Q01844.1	EYA2 O00167.1	EZH2 Q15910.1
FABP7 O15540.1	FAM133A Q8N9E0.1	FAM13A O94988.1	FAM46D Q8NEK8.1
FAM58BP P0C7Q3.1	FANCG O15287.1	FATE1 Q969F0.1	FBXO39 Q8N4B4.1
FBXW11 Q9UKB1.1	FCHSD2 O94868.1	FER P16591.1	FES P07332.1
FEV Q99581.1	FGF10 O15520.1	FGF23 Q9GZV9.1	FGF3 P11487.1

FGF4 P08620.1	FGF5 P12034.1	FGFR1 P11362.1	FGFR2 P21802.1
FGFR3 P22607.1	FGFR4 P22455.1	FGR P09769.1	FLI1 Q01543.1
FLT3 P36888.1	FMNL1 O95466.1	FMOD Q06828.1	FMR1NB Q8N0W7.1
FN1 P02751.1	Fn14 Q9NP84.1	FNIP2 Q9P278.1	FOLR1 P15328.1
FOS P01100.1	FosB P53539.1	FOSL1 P15407.1	FOXM1 Q08050.1
FOXO1 Q12778.1	FOXO3 O43524.1	FRAT1 Q92837.1	FRMD3 A2A2Y4.1
FSIP1 Q8NA03.1	FSIP2 Q5CZC0.1	FSTL3 O95633.1	FTHL17 Q9BXU8.1
FUNDC2 Q9BWH2.1	FUS P35637.1	FUT1 P19526.1	FUT3 P21217.1
FYN P06241.1	GAB2 Q9UQC2.1	GADD45G O95257.1	GAGE-1 Q13065.1
GAGE12B/C/D/E A1L429.1	GAGE12F P0CL80.1	GAGE12G P0CL81.1	GAGE12H A6NDE8.1
GAGE12I P0CL82.1	GAGE12J A6NER3.1	GAGE-2 Q6NT46.1	GAGE-3 Q13067.1
GAGE-4 Q13068.1	GAGE-5 Q13069.1	GAGE-6 Q13070.1	GAGE-7 O76087.1
GAGE-8 Q9UEU5.1	GALGT2 Q00973.1	GAS7 O60861.1	GASZ Q8WWH4.1
GATA-3 P23771.1	GBU4-5 Q587J7.1	GCDFP-15 P12273.1	GFAP P14136.1
GFI1 Q99684.1	Ghrelin Q9UBU3.1	GHSR Q92847.1	GIPC1 O14908.1
GITR Q9Y5U5.1	GKAP1 Q5VSY0.1	GLI1 P08151.1	Glypican-3 P51654.1
GML Q99445.1	GNA11 P29992.1	GNAQ P50148.1	GNB2L1 P63244.1
GOLGA5 Q8TBA6.1	gp100 P40967.1	gp75 P17643.1	Gp96 P14625.1
GPAT2 Q6NUI2.1	GPATCH2 Q9NW75.1	GPC-3 P51654.1	GPNMB Q14956.1
GPR143 P51810.1	GPR89A B7ZAQ6.1	GRB2 P62993.1	GRP78 P11021.1
GUCY1A3 Q02108.1	H3F3A P84243.1	HAGE Q9NXZ2.1	hANP P01160.1
HBEGF Q99075.1	hCG-beta P01233.1	HDAC1 Q13547.1	HDAC2 Q92769.1
HDAC3 O15379.1	HDAC4 P56524.1	HDAC5 Q9UQL6.1	HDAC6 Q9UBN7.1
HDAC7 Q8WUI4.1	HDAC8 Q9BY41.1	HDAC9 Q9UKV0.1	HEATR1 Q9H583.1
Hepsin P05981.1	Her2/neu P04626.1	HERC2 O95714.1	HERV-K104 P61576.1
HEXB P07686.1	HEXIM1 O94992.1	HGRG8 Q9Y5A9.1	HIPK2 Q9H2X6.1
HJURP Q8NCD3.1	HMGB1 P09429.1	HMOX1 P09601.1	HNRPL P14866.1
HOM-TES-85 Q9P127.1	HORMAD1 Q86X24.1	HORMAD2 Q8N7B1.1	HPSE Q9Y251.1
HPV16 E6 P03126.1	HPV16 E7 P03129.1	HPV18 E6 P06463.1	HPV18 E7 P06788.1
HRAS P01112.1	HSD17B13 Q7Z5P4.1	HSP105 Q92598.1	HSP60 P10809.1
HSPA1A P08107.1	HSPB9 Q9BQS6.1	HST-2 P10767.1	HT001 Q2TB18.1
hTERT O14746.1	HUS1 O60921.1	ICAM-1 P05362.1	IDH1 O75874.1
IDO1 P14902.1	IER3 P46695.1	IGF1R P08069.1	IGFS11 Q5DX21.1
IL13RA2 Q14627.1	IMP-3 Q9NV31.1	ING3 Q9NXR8.1	INPPL1 O15357.1
INTS6 Q9UL03.1	IRF4 Q15306.1	IRS4 O14654.1	ITGA5 P08648.1
ITGB8 P26012.1	ITPA Q9BY32.1	ITPR2 Q14571.1	JAK2 O60674.1
JAK3 P52333.1	JARID1B Q9UGL1.1	JAZF1 Q86VZ6.1	JNK1 P45983.1
JNK2 P45984.1	JNK3 P53779.1	JTB O76095.1	JUN P05412.1
JUP P14923.1	K19 P08727.1	KAAG1 Q9UBP8.1	Kallikrein 14 Q9P0G3.1
Kallikrein 4 Q9Y5K2.1	KAT6A Q92794.1	KDM1A O60341.1	KDM5A P29375.1
KIAA0100 Q14667.1	KIAA0336 Q8IWJ2.1	KIAA1199 Q8WUJ3.1	KIAA1641 A6QL64.1
KIF11 P52732.1	KIF1B O60333.1	KIF20A O95235.1	KIT P10721.1
KLF4 O43474.1	KLHL41 O60662.1	KLK10 O43240.1	KMT2D O14686.1
KOC1 O00425.1	K-ras P01116.1	KRIT1 O00522.1	KW-12 P62913.1
KW-2 Q96RS0.1	KW-5 (SEBD4) Q9H0Z9.1	KW-7 O75475.1	L1CAM P32004.1
L53 Q96EL3.1	L6 Q9BTT4.1	LAG3 P18627.1	Lage-1 O75638.1
LATS1 O95835.1	LATS2 Q9NRM7.1	LCMT2 O60294.1	LCP1 P13796.1
LDHC P07864.1	LDLR P01130.1	LEMD1 Q68G75.1	Lengsin Q5TDP6.1
LETMD1 Q6P1Q0.1	LGALS3BP Q08380.1	LGALS8 O00214.1	LIN7A O14910.1

LIPI Q6XZB0.1	LIV-1 Q13433.1	LLGL1 Q15334.1	LMO1 P25800.1
LMO2 P25791.1	LMP1 P03230.1	LMP2 P13285.1	LOC647107 Q8TAI5.1
LOXL2 Q9Y4K0.1	LRP1 Q07954.1	LRRN2 O75325.1	LTF P02788.1
LTK P29376.1	LZTS1 Q9Y250.1	LY6K Q17RY6.1	LYN P07948.1
LYPD6B Q8NI32.1	MAEA Q7L5Y9.1	MAEL Q96JY0.1	MAF O75444.1
MAFF Q9ULX9.1	MAFG O15525.1	MAFK O60675.1	MAGE-A1 P43355.1
MAGE-A10 P43363.1	MAGE-A11 P43364.1	MAGE-A12 P43365.1	MAGE-A2 P43356.1
MAGE-A2B Q6P448.1	MAGE-A3 P43357.1	MAGE-A4 P43358.1	MAGE-A5 P43359.1
MAGE-A6 P43360.1	MAGE-A8 P43361.1	MAGE-A9 P43362.1	MAGE-B1 P43366.1
MAGE-B2 O15479.1	MAGE-B3 O15480.1	MAGE-B4 O15481.1	MAGE-B5 Q9BZ81.1
MAGE-B6 Q8N7X4.1	MAGE-C1 O60732.1	MAGE-C2 Q9UBF1.1	MAGE-C3 Q8TD91.1
mammaglobin-A Q13296.1	MANF P55145.1	MAP2K2 P36507.1	MAP2K7 O14733.1
MAP3K7 O43318.1	MAP4K5 Q9Y4K4.1	MART1 Q16655.1	MART-2 Q5VTY9.1
MAS1 P04201.1	MC1R Q01726.1	MCAK Q99661.1	MCF2 P10911.1
MCF2L O15068.1	MCL1 Q07820.1	MCTS1 Q9ULC4.1	MCSP Q6UVK1.1
MDK P21741.1	MDM2 Q00987.1	MDM4 O15151.1	ME1 P48163.1
ME491 P08962.1	MECOM Q03112.1	MELK Q14680.1	MEN1 O00255.1
MERTK Q12866.1	MET P08581.1	MFGE8 Q08431.1	MFHAS1 Q9Y4C4.1
MFI2 P08582.1	MGAT5 Q09328.1	Midkine P21741.1	MIF P14174.1
MKI67 P46013.1	MLH1 P40692.1	MLL Q03164.1	MLLT1 Q03111.1
MLLT10 P55197.1	MLLT11 Q13015.1	MLLT3 P42568.1	MLLT4 P55196.1
MLLT6 P55198.1	MMP14 P50281.1	MMP2 P08253.1	MMP7 P09237.1
MMP9 P14780.1	MOB3B Q86TA1.1	MORC1 Q86VD1.1	MPHOSPH1 Q96Q89.1
MPL P40238.1	MRAS O14807.1	MRP1 P33527.1	MRP3 O15438.1
MRPL28 Q13084.1	MRPL30 Q8TCC3.1	MRPS11 P82912.1	MSLN Q13421.1
MTA1 Q13330.1	MTA2 O94776.1	MTA3 Q9BTC8.1	MTCP1 P56278.1
MTSS1 O43312.1	MUC-1 P15941.1	MUC-2 Q02817.1	MUC-3 Q02505.1
MUC-4 Q99102.1	MUC-5AC P98088.1	MUC-6 Q6W4X9.1	MUM1 Q2TAK8.1
MUM2 Q9Y5R8.1	MYB P10242.1	MYC P01106.1	MYCL P12524.1
MYCLP1 P12525.1	MYCN P04198.1	MYD88 Q99836.1	MYEOV Q96EZ4.1
MYO1B O43795.1	NA88-A P0C5K6.1	NAE1 Q13564.1	Napsin-A O96009.1
NAT6 Q93015.1	NBAS A2RRP1.1	NBPF12 Q5TAG4.1	NCOA4 Q13772.1
NDC80 O14777.1	NDUFC2 O95298.1	Nectin-4 Q96NY8.1	NEK2 P51955.1
NEMF O60524.1	NENF Q9UMX5.1	NEURL1 O76050.1	NFIB O00712.1
NFKB2 Q00653.1	NF-X1 Q12986.1	NFYC Q13952.1	NGAL P80188.1
NGEP Q6IWH7.1	NKG2D-L1 Q9BZM6.1	NKG2D-L2 Q9BZM5.1	NKG2D-L3 Q9BZM4.1
NKG2D-L4 Q8TD07.1	NKX3.1 Q99801.1	NLGN4X Q8N0W4.1	NLRP4 Q96MN2.1
NNMT P40261.1	NOL4 O94818.1	NOTCH2 Q04721.1	NOTCH3 Q9UM47.1
NOTCH4 Q99466.1	NOV P48745.1	NPM1 P06748.1	NR6A1 Q15406.1
N-RAS P01111.1	NRCAM Q92823.1	NRP1 O14786.1	NSE1 Q96KN4.1
NSE2 Q96KN1.1	NTRK1 P04629.1	NUAK1 O60285.1	NUGGC Q68CJ6.1
NXF2 Q9GZY0.1	NXF2B Q5JRM6.1	NY-BR-1 Q9BXX3.1	NYD-TSPG Q9BWV7.1
NY-ESO-1 P78358.1	NY-MEL-1 P57729.1	OCA2 Q04671.1	ODF1 Q14990.1
ODF2 Q5BJF6.1	ODF3 Q96PU9.1	ODF4 Q2M2E3.1	OGG1 O15527.1
OGT O15294.1	OIP5 O43482.1	OS9 Q13438.1	OTOA Q05BM7.1
OX40 P43489.1	OX40L P23510.1	P53 P04637.1	P56-LCK P06239.1
PA2G4 Q9UQ80.1	PAGE1 O75459.1	PAGE2 Q7Z2X2.1	PAGE2B Q5JRK9.1
PAGE3 Q5JUK9.1	PAGE4 O60829.1	PAGE5 Q96GU1.1	PAK2 Q13177.1
PANO1 I0J062.1	PAP Q06141.1	PAPOLG Q9BWT3.1	PARK2 O60260.1
PARK7 Q99497.1	PARP12 Q9H0J9.1	PASD1 Q8IV76.1	PAX3 P23760.1
PAX5 Q02548.1	PBF P00751.1	PBK Q96KB5.1	PBX1 P40424.1

PCDC1 Q15116.1	PCM1 Q15154.1	PCNXL2 A6NKB5.1	PDGFB P01127.1
PDGFRA P16234.1	PEPP2 Q9HAU0.1	PGF P49763.1	PGK1 P00558.1
PHLDA3 Q9Y5J5.1	PHLPP1 O60346.1	PIAS1 O75925.1	PIAS2 O75928.1
PIK3CA P42336.1	PIK3CD O00329.1	PIK3R2 O00459.1	PIM1 P11309.1
PIM2 Q9P1W9.1	PIM3 Q86V86.1	PIR O00625.1	PIWIL1 Q96J94.1
PIWIL2 Q8TC59.1	PIWIL3 Q7Z3Z3.1	PIWIL4 Q7Z3Z4.1	PKN3 Q6P5Z2.1
PLA2G16 P53816.1	PLAC1 Q9HBJ0.1	PLAG1 Q6DJT9.1	PLEKHG5 O94827.1
PLK3 Q9H4B4.1	PLS3 P13797.1	PLVAP Q9BX97.1	PLXNB1 O43157.1
PLXNB2 O15031.1	PML P29590.1	PML-RARA Q96QH2.1	POTEA Q6S8J7.1
POTEB Q6S5H4.1	POTEC B2RU33.1	POTED Q86YR6.1	POTEE Q6S8J3.1
POTEG Q6S5H5.1	POTEH Q6S545.1	PP2A P63151.1	PPAPDC1B Q8NEB5.1
PPFIA1 Q13136.1	PPIG Q13427.1	PPP2R1B P30154.1	PRAME P78395.1
PRDX5 P30044.1	PRKAA1 Q13131.1	PRKCI P41743.1	PRM1 P04553.1
PRM2 P04554.1	PRMT3 O60678.1	PRMT6 Q96LA8.1	PDL1 Q9NZQ7.1
PROM1 O43490.1	PRSS54 Q6PEW0.1	PRSS55 Q6UWB4.1	PRTN3 P24158.1
PRUNE Q86TP1.1	PRUNE2 Q8WUY3.1	PSA P07288.1	PSCA D3DWI6.1
PSMA Q04609.1	PSMD10 O75832.1	PSGR Q9H255.1	PSP-94 Q1L6U9.1
PTEN P60484.1	PTH-rP P12272.1	PTK6 Q13882.1	PTPN20A Q4JDL3.1
PTPRK Q15262.1	PTPRZ P23471.1	PTTG-1 O95997.1	PTTG2 Q9NZH5.1
PTTG3 Q9NZH4.1	PXDNL A1KZ92.1	RAB11FIP3 O75154.1	RAB8A P61006.1
RAD1 O60671.1	RAD17 O75943.1	RAD51C O43502.1	RAF1 P04049.1
RAGE-1 Q9UQ07.1	RAP1A P62834.1	RARA P10276.1	RASSF10 A6NK89.1
RB1 P06400.1	RBL2 Q08999.1	RBM46 Q8TBY0.1	RBP4 P02753.1
RCAS1 O00559.1	RCVRN P35243.1	RECQL4 O94761.1	RET P07949.1
RGS22 Q8NE09.1	RGS5 O15539.1	RHAMM O75330.1	RhoC P08134.1
RHOXF2 Q9BQY4.1	RL31 P62888.1	RNASET2 O00584.1	RNF43 Q68DV7.1
RNF8 O76064.1	RON Q04912.1	ROPN1A Q9HAT0.1	ROR1 Q01973.1
RPA1 O95602.1	RPL10A P62906.1	RPL7A P62424.1	RPS2 P15880.1
RPS6KA5 O75582.1	RPSA P08865.1	RQCD1 Q92600.1	RRAS2 P62070.1
RSL1D1 O76021.1	RTKN Q9BST9.1	RUNX1 Q01196.1	RUNX2 Q13950.1
RYK P34925.1	SAGE1 Q9NXZ1.1	SART2 Q9UL01.1	SART3 Q15020.1
SASH1 O94885.1	sCLU P10909.1	SCRN1 Q12765.1	SDCBP O00560.1
SDF-1 P48061.1	SDHD O14521.1	SEC31A O94979.1	SEC63 Q9UGP8.1
Semaphorin 4D Q92854.1	SEMG1 P04279.1	SFN P31947.1	SH2B2 O14492.1
SH2D1B O14796.1	SH3BP1 Q9Y3L3.1	SHB Q15464.1	SHC3 Q92529.1
SIRT2 Q8IXJ6.1	SIVA1 O15304.1	SKI P12755.1	SLBP A9UHW6.1
SLC22A10 Q63ZE4.1	SLC25A47 Q6Q0C1.1	SLC35A4 Q96G79.1	SLC45A3 Q96JT2.1
SLC4A1AP Q9BWU0.1	SLCO6A1 Q86UG4.1	SLITRK6 Q9H5Y7.1	Sm23 P27701.1
SMAD5 Q99717.1	SMAD6 O43541.1	SMO Q99835.1	Smt3B P61956.1
SNRPD1 P62314.1	SOS1 Q07889.1	SOX-2 P48431.1	SOX-6 P35712.1
SOX-11 P35716 .1	SPA17 Q15506.1	SPACA3 Q8IXA5.1	SPAG1 Q07617.1
SPAG17 Q6Q759.1	SPAG4 Q9NPE6.1	SPAG6 O75602.1	SPAG8 Q99932.1
SPAG9 O60271.1	SPANXA1 Q9NS26.1	SPANXB Q9NS25.1	SPANXC Q9NY87.1
SPANXD Q9BXN6.1	SPANXE Q8TAD1.1	SPANXN1 Q5VSR9.1	SPANXN2 Q5MJ10.1
SPANXN3 Q5MJ09.1	SPANXN4 Q5MJ08.1	SPANXN5 Q5MJ07.1	SPATA19 Q7Z5L4.1
SPEF2 Q9C093.1	SPI1 P17947.1	SPINLW1 O95925.1	SPO11 Q9Y5K1.1
SRC P12931.1	SSPN Q14714.1	SSX-1 Q16384.1	SSX-2 Q16385.1
SSX-3 Q99909.1	SSX-4 O60224.1	SSX-5 O60225.1	SSX-6 Q7RTT6.1
SSX-7 Q7RTT5.1	SSX-9 Q7RTT3.1	ST18 O60284.1	STAT1 P42224.1
STEAP1 Q9UHE8.1	STK11 Q15831.1	STK25 O00506.1	STK3 Q13188.1
STN Q9H668.1	SUPT7L O94864.1	Survivin O15392.1	SUV39H1 O43463.1
SYCE1 Q8N0S2.1	SYCP1 Q15431.1	SYCP3 Q8IZU3.1	SYT Q15532.1
TA-4 Q96RI8.1	TACC1 O75410.1	TAF1B Q53T94.1	TAF4 O00268.1
TAF7L Q5H9L4.1	TAG-1 Q02246.1	TAL1 P17542.1	TAL2 Q16559.1
TAPBP O15533.1	TATI P00995.1	TAX1BP3 O14907.1	TBC1D3 Q8IZP1.1

TBP-1	P17980.1	TCL1A	P56279.1	TCL1B	O95988.1	TDHP	Q9BT92.1
TDRD1	Q9BXT4.1	TDRD4	Q9BXT8.1	TDRD6	O60522.1	TEKT5	Q96M29.1
TEX101	Q9BY14.1	TEX14	Q8IWB6.1	TEX15	Q9BXT5.1	TEX38	Q6PEX7.1
TF	P02787.1	TFDP3	Q5H9I0.1	TFE3	P19532.1	TGFBR1	P36897.1
TGFBR2	P37173.1	THEG	Q9P2T0.1	TIE2	Q02763.1	TIPRL	O75663.1
TLR2	O60603.1	TMEFF1	Q8IYR6.1	TMEFF2	Q9UIK5.1	TMEM108	Q6UXF1.1
TMEM127	O75204.1	TMPRSS12	Q86WS5.1	TNC	P24821.1	TNFRSF17	Q02223.1
TNFSF15	O95150.1	TNK2	Q07912.1	TOMM34	Q15785.1	TOP2A	P11388.1
TOP2B	Q02880.1	TOR3A	Q9H497.1	TP73	O15350.1	TPA1	8N543.1
TPGS2	Q68CL5.1	TPI1	P60174.1	TPL2	P41279.1	TPM4	P67936.1
TPO	P40225.1	TPPP2	P59282.1	TPR	P12270.1	TPTE	P56180.1
TRAF5	O00463.1	TRAG-3	Q9Y5P2.1	TRGC2	P03986.1	TRIM24	O15164.1
TRIM37	O94972.1	TRIM68	Q6AZZ1.1	TRPM8	Q7Z2W7.1	TSGA10	Q9BZW7.1
TSP50	Q9UI38.1	TSPAN6	O43657.1	TSPY1	Q01534.1	TSPY2	A6NKD2.1
TSPY3	Q6B019.1	TSPYL1	Q9H0U9.1	TSSK6	Q9BXA6.1	TTC23	Q5W5X9.1
TTK	P33981.1	TULP2	O00295.1	TUSC2	O75896.1	TWEAK	O43508.1
TXNIP	Q9H3M7.1	TYMS	P04818.1	TYR	P14679.1	U2 snRNP B	P08579.1
U2AF1	Q01081.1	UBD	O15205.1	UBE2A	P49459.1	UBE2C	O00762.1
UBE2V1	Q13404.1	UBE4B	O95155.1	UBR5	O95071.1	UBXD5	Q5T124.1
UFL1	O94874.1	URI1	O94763.1	URLC10	Q17RY6.1	UROC1	Q96N76.1
USP2	O75604.1	USP4	Q13107.1	VAV1	P15498.1	VCX3A	Q9NNX9.1
VEGFR1	P17948.1	VEGFR2	P35968.1	VHL	P40337.1	VIM	P08670.1
VWA5A	O00534.1	WHSC2	Q9H3P2.1	WISP1	O95388.1	WNK2	Q9Y3S1.1
WNT10B	O00744.1	WNT3	P56703.1	WNT-5a	P41221.1	WT1	P19544.1
WWP1	Q9H0M0.1	XAGE-1	Q9HD64.1	XAGE-2	Q96GT9.1	XAGE-3	Q8WTP9.1
XAGE-4	Q8WWM0.1	XAGE-5	Q8WWM1.1	XBP1	P17861.1	XPO1	O14980.1
XRCC3	O43542.1	YB-1	P67809.1	YEATS4	O95619.1	YES1	P07947.1
YKL-40	P36222.1	ZBTB7A	O95365.1	ZBTB7C	A1YPR0.1	ZEB1	P37275.1
ZFYVE19	Q96K21.1	ZNF165	P49910.1	ZNF185	O15231.1	ZNF217	O75362.1
ZNF320	A2RRD8.1	ZNF395	Q9H8N7.1	ZNF645	Q8N7E2.1	ZUBR1	Q5T4S7.1
ZW10	O43264.1	ZWINT	O95229.1				

Table 3 - LIST OF ACCESSION NUMBERS FOR VIRAL ANTIGENS FROM IEDB

	Q76R62.1	P03182.1	P09258.1	P09310.1	P03227.1	P89466.1	P04601.1
P13285.1	P09991.1	P03468.1	A2T3Q0.1	P0C6X7.1	P89448.1	P12978.1	P09257.1
P50641.1	P14075.1	20178567.1	Q01023.1	P03188.1	P04585.1	P0C767.1	P12977.1
P89467.1	Q9W850.1	Q00683.1	P04591.1	P03211.1	9628706.1	P03460.1	P08666.1
P03485.1	Q04360.1	Q913Y7.1	P89449.1	Q81871.1	P03452.1	P17763.1	P89430.1
P03410.1	P04012.1	P27958.1	Q6WB99.1	P25212.1	Q9PZT1.1	P68593.1	P03203.1
P29996.1	9629374.1	P59633.1	O42053.1	P0C6L3.1	P59635.1	Q9YZN9.1	Q6WB95.1
P10233.1	P89475.1	Q6WB98.1	Q6SW67.1	Q7TFA0.1	P0CK17.1	P59594.1	1980491.1
P14079.1	P15423.1	1891762.1	P09259.1	P09269.1	Q77Q38.1	Q786F2.1	Q6SW99.1
P24771.1	F5HB98.1	9629370.1	P68336.1	P03300.1	1980486.1	Q69027.1	P28284.1
P13290.1	9626585.1	P06923.1	P14076.1	P03346.1	O42062.1	P07566.1	P03204.1
Q69091.1	P09255.1	P03206.1	O36634.1	P10205.1	F5HCM1.1	P0CK16.1	Q6WB97.1
Q85601.1	P89468.1	Q69467.1	P03218.1	Q786F3.1	P59637.1	1891763.1	Q6WB94.1
P03231.1	Q9IK92.1	Q6WBA1.1	P03466.1	P14335.1	P26670.1	Q9PZT0.1	1985356.1
Q2HR63.1	P59634.1	Q6SW59.1	P03277.1	P59595.1	Q69028.1	P03383.1	P03261.1
P03200.1	P04578.1	P06484.1	F5HC97.1	S5TC82.1	P18095.1	Q96895.1	P18094.1
9629372.1	P50791.1	P03230.1	P13845.1	9629712.1	P03209.1	P03129.1	Q76R61.1
P03228.1	P0C206.1	Q9WMB5.1	P03226.1	Q9QR69.1	O36633.1	O42049.1	P03496.1
P03428.1	P03431.1	P0C0U1.1	P03433.1	P03508.1	1980456.1	P0C739.1	P69726.1
P69723.1	1980490.1	532129755.1	P03120.1	P04020.1	P06922.1	P03114.1	P03314.1
P06790.1	P06788.1	P06927.1	P03101.1	P03107.1	P06794.1	530787712.1	P04013.1
Q80872.1	P04014.1	P03126.1	P36811.1	P06463.1	P26554.1	P04016.1	P14078.1
P03191.1	1980471.1	P06821.1	P0C797.1	F5HF49.1	P0C045.1	P04296.1	P04485.1
P10230.1	P10221.1	P06487.1	P10215.1	P04293.1	P10211.1	P10209.1	P10225.1

P10224.1	P10238.1	P10185.1	P08392.1	P10231.1	P06492.1	P04290.1	P08393.1
P08543.1	P10210.1	P08617.1	F5HB53.1	P04019.1	P04015.1	P89442.1	P89452.1
P89462.1	P59632.1	O36635.1	P07210.1	Q83884.1	Q8JUX5.1	P03089.1	Q66479.1
P03185.1	P0CAP6.1	P04618.1	56160929.1	1980519.1	P08669.1	P14348.1	P03212.1
P03179.1	45617-other.1	1511872.1	302317869.1	P69899.1	P09247.1	Q05127.1	P18272.1
Q9YMG2.1	Q05128.1	302371215.1	302371218.1	Q5XX08.1	302371214.1	P14336.1	138948-other.1
P08292.1	1803956.1	P35253.1	1891726.1	P09308.1	P03189.1	667489389.1	P09272.1
34365530.1	Q05320.1	P59596.1	P32886.1	55097.1	P03316.1	P03276.1	Q81870.1
Q81862.1	64320.1	1933190.1					

Table 4 -LIST OF ACCESSION NUMBERS FOR BACTERIAL ANTIGENS FROM IEDB

	B8ZUD1.1	P09621.1	P9WPE5.1	Q2GI62.1	P0A5B8.1	O50443.1	Q5NEZ3.1
P9WQF5.1	P9WK95.1	O05311.1	P9WQD7.1	P9WKG3.1	P9WHE5.1	P0CD83.1	P9WHB9.1
P9WH91.1	P9WHE3.1	P9WNK7.1	A0A0F3MKF3.1	A1JIP3.1	B2RKS6.1	P0A1D3.1	P0A6F5.1
P0C0Z7.1	P0C923.1	P61439.1	Q9Z708.1	P0A521.1	P9WPE7.1	Q79FJ2.1	B8ZR84.1
I6Y3P5.1	Q2FYP2.1	P9WG41.1	P96890.1	O06625.1	I6X654.1	Q8YIE1.1	P9WQ81.1
I6XWA1.1	P11311.1	O53900.1	P9WIR7.1	P9WQB1.1	B8ZUC6.1	O06802.1	P9WMK1.1
P9WG37.1	Q2FWC4.1	Q2GGE3.1	O33347.1	P9WJ09.1	P9WJ11.1	P9WF23.1	O69703.1
I6X4K0.1	B2RM93.1	P71888.1	P9WFW3.1	P9WPV1.1	P9WPU7.1	P9WPV3.1	P9WPU5.1
O50391.1	P9WID7.1	P9WPC3.1	P96901.1	O84848.1	Q2FUX4.1	A0A0M1YNY3.1	P49944.1
P9WPQ9.1	Q45010.1	Q2FZK7.1	P9WMN3.1	P9WPQ1.1	Q45013.1	O53666.1	Q5NEH1.1
P9WHR5.1	P9WIE5.1	Q5NEQ3.1	P9WNF3.1	F2QBN0.1	B8ZTB7.1	P0C922.1	P9WMJ9.1
Q5NGW2.1	P01556.1	Q8DMZ4.1	P33768.1	Q2FUY2.1	Q5NG56.1	X8CE55.1	Q5NGE4.1
P94973.1	O06827.1	P96872.1	I6X9Y7.1	I6XFZ8.1	O50442.1	O53697.1	O53978.1
P95137.1	P95144.1	O53519.1	Q79FZ8.1	P9WJF5.1	P71629.1	P9WJS3.1	P9WPB7.1
Q7D9T1.1	P9WHS1.1	O06393.1	P9WP69.1	P9WPN5.1	P9WNX3.1	O53380.1	I6YAU3.1
P0A4V2.1	P9WQP3.1	P0C2T2.1	P9WQP1.1	P9WQN9.1	O53311.1	P9WIS7.1	O06159.1
H2GU79.1	Q2G2Q0.1	P9WNV1.1	P9WNV5.1	Q8YE98.1	Q59191.1	P9WGY7.1	P9WGY9.1
Q2G2W1.1	P9WGH1.1	P9WNG9.1	P9WNG7.1	O84591.1	Q9Z7A6.1	P9WGR1.1	P96404.1
I6YGS0.1	Q6MX18.1	P9WNK5.1	O53692.1	P9WNK3.1	P9WNK1.1	P9WNJ9.1	P9WNJ7.1
P9WNJ5.1	P9WNJ3.1	P9WNJ1.1	P9WNI9.1	P96903.1	P9WNB1.1	P9WJE1.1	P9WJD9.1
P9WJD7.1	P9WJD3.1	P9WJC5.1	P9WJC3.1	P9WJC1.1	P9WNQ3.1	P9WJE5.1	P9WJC7.1
O84646.1	I6YDV4.1	P11439.1	Q5NFJ1.1	P9WNE5.1	P14738.1	P11089.1	H7C7G3.1
L7N6B9.1	I6XFI7.1	O05578.1	P96218.1	P9WN39.1	P9WN59.1	Q8YBI3.1	P9WN83.1
P9WJA9.1	P9WMY9.1	Q5NH51.1	O53673.1	P9WIP9.1	P0CE15.1	P72041.1	Q5NEM8.1
Q5NI16.1	P9WJA3.1	P0A4Q1.1	P9WIP1.1	P9WIN9.1	P9WNF5.1	O50846.1	Q59947.1
H7C7N8.1	Q5NEC6.1	O84606.1	P9WQJ9.1	P9WQJ7.1	P9WQ71.1	O53611.1	P9WKL1.1
P9WKJ7.1	D5V9Y8.1	P0CC04.1	P23700.1	P9WJN5.1	Q5NHJ0.1	Q5NEY9.1	P15917.1
Q2G155.1	O34094.1	Q8F8E1.1	O69661.1	H6MMU4.1	P9WK61.1	P9WK55.1	Q8YGS9.1
O50811.1	P9WQ59.1	P9WIN7.1	P9WIR1.1	O50430.1	D5VCH6.1	Q5NHI7.1	P9WFU9.1
I6XFY8.1	B2RH54.1	Q46409.1	P30690.1	A0A0J5IWN3.1	A0PSI5.1	A4TAC4.1	B1MB69.1
B2HSY2.1	B8ZSN3.1	E4WHS0.1	P9WK17.1	V5XE39.1	I6X7G8.1	I6Y461.1	I6YGB1.1
I6YC99.1	Q79FY7.1	I6X5Z8.1	I6Y479.1	I6YA32.1	O05461.1	Q2G1E2.1	P9WK19.1
I6YAW3.1	Q5NGG4.1	O51624.1	P9WJW5.1	Q50584.1	B2RHG1.1	Q5NFL7.1	P9WQN7.1
P9WHH3.1	O84639.1	Q5NF24.1	P9WJH1.1	P9WJH5.1	O53203.1	P55969.1	O50418.1
Q5NGE0.1	H7C7K8.1	O54584.1	G1UB30.1	Q5NH85.1	G1UB25.1	P0A3N8.1	E1X6Y5.1
Q5NEP7.1	Q8YHH0.1	P38006.1	P43838.1	P43839.1	P0CL67.1	P0CL66.1	Q0SLZ0.1
Q07337.1	G5IXI6.1	O07721.1	O53254.1	P75330.1	I6Y936.1	L7N649.1	L7N656.1
L7N693.1	Q79FK4.1	Q79FR3.1	Q79FR5.1	Q79G04.1	Q79FS8.1	Q6MWX1.1	Q79FV6.1
Q79FS5.1	Q79FQ7.1	Q79FP3.1	Q79FP2.1	Q79FK9.1	Q79FE6.1	I6XEF1.1	Q79FD4.1
Q6MX26.1	Q6MX50.1	L7N680.1	O53695.1	I6X8R2.1	O53246.1	I6Y0L1.1	Q2G282.1
P14283.1	P04977.1	P9WMX7.1	P9WFR1.1	P9WN09.1	O86345.1	P9WGU1.1	P9WGT9.1
P9WGT7.1	P9WPF7.1	P9WIB3.1	P9WMM9.1	P9WHM5.1	P9WQE9.1	Q8DQ08.1	Q8DQ07.1
I6Y231.1	P9WHV9.1	O05877.1	O07236.1	O86370.1	O06404.1	O06410.1	B8ZRL2.1
O06807.1	O33269.1	Q79FA9.1	Q79FK6.1	Q8VKN2.1	L7N675.1	Q79FK5.1	L0T7Y7.1
Q79FI9.1	Q79FE1.1	Q6MWX9.1	O84616.1	O84647.1	P9WQ27.1	O84288.1	I6X9S5.1

P9WJW3.1	P9WPS9.1	P95149.1	O53632.1	I6Y293.1	L0T243.1	P9WP43.1	P9WKC9.1
P96402.1	P71810.1	O06417.1	P96365.1	L0T5B2.1	P96264.1	P9WJK5.1	P9WJQ9.1
O84419.1	O84818.1	Q8YG32.1	O06608.1	O07175.1	P9WGA3.1	O53323.1	P96354.1
P9WIM9.1	B8ZRT2.1	P9WK93.1	P13423.1	O84583.1	P9WG63.1	P9WIM1.1	P9WKJ3.1
P9WNZ7.1	P9WK31.1	Q50701.1	P9WID3.1	Q8YC41.1	P9WPL3.1	P9WNI3.1	P9WNI7.1
P9WNI5.1	P9WQ49.1	P9WMG1.1	Q2GGR3.1	P9WK71.1	O33192.1	P9WND5.1	P9WFL9.1
P9WMB7.1	P9WJ79.1	P9WND7.1	Q63RA7.1	Q63ID0.1	I6YET7.1	Q9S010.1	P9WGC9.1
Q50700.1	Q5NFR6.1	P9WGK3.1	P9WHI1.1	P9WHV3.1	Q5NIA7.1	P9WG27.1	P9WF73.1
P9WGA1.1	P9WIB9.1	P9WGL3.1	O51381.1	P9WI83.1	P9WI79.1	P9WFT7.1	Q8YGS6.1
P05788.1	P17835.1	P9WIK9.1	Q5NHP7.1	P9WJU5.1	P9WGE7.1	Q2G2B2.1	P04958.1
P9WG67.1	P9WKE1.1	O07226.1	P9WJ13.1	P9WHF3.1	P9WF43.1	Q7D7L0.1	P9WMF9.1
P9WGN1.1	P9WKJ9.1	P60230.1	P9WKH7.1	O53699.1	P9WHT7.1	P9WJS5.1	Q5NII0.1
Q8YDZ3.1	Q9RPX7.1	P9WN67.1	O05576.1	Q5NHL4.1	P9WN15.1	P9WMD5.1	P9WMF5.1
P9WG85.1	P9WJW7.1	P9WIH1.1	P9WIG1.1	P9WIG3.1	P9WIF5.1	P9WIF1.1	P9WIE7.1
P9WHW9.1	P9WI41.1	P9WI39.1	P9WI37.1	P9WI25.1	Q11031.1	P9WI47.1	P9WI23.1
P9WI19.1	P9WI11.1	P9WI45.1	P9WI07.1	P9WI05.1	Q79FH3.1	P9WI43.1	P9WHZ7.1
P9WHZ5.1	P9WHZ3.1	P9WHY9.1	P9WHY7.1	P9WHY5.1	Q6MX07.1	P9WHY3.1	Q6MWY2.1
Q50703.1	P9WHX3.1	P96221.1	Q7D589.1	P9WMA3.1	P9WKW1.1	P9WKS9.1	P9WM29.1
P9WGC1.1	P9WLZ5.1	P9WLZ3.1	P9WLX1.1	P9WLV9.1	P9WLS7.1	P9WLQ1.1	P9WLJ1.1
P9WLH9.1	P9WLF3.1	P9WL97.1	P9WL87.1	P9WL85.1	P9WL83.1	P9WL67.1	P9WL63.1
P9WL51.1	P9WL47.1	P9WNH3.1	P9WGL7.1	P9WQM5.1	P9WPD9.1	A0A098A1N7.1	A0A098A2B0.1
A2RGM0.1	A5LVF6.1	A5MKZ9.1	B8ZQI8.1	B8ZQM3.1	B8ZQT5.1	B8ZR82.1	B8ZRH1.1
B8ZS71.1	B8ZS85.1	B8ZS86.1	B8ZSJ5.1	B8ZSL3.1	B8ZSL7.1	B8ZSM6.1	B8ZT30.1
B8ZTD0.1	B8ZTS2.1	B8ZTV5.1	B8ZU53.1	B8ZUA4.1	B8ZUE5.1	B8ZUF0.1	B8ZUT6.1
B8ZUX6.1	C0R9U8.1	C6DPT8.1	C6DQ35.1	E1XJN6.1	G8W6L3.1	G8W6L7.1	G8W6U7.1
H6MNY3.1	H6MQD5.1	H8HRN0.1	H8HW90.1	H8L8K3.1	I6TQ53.1	I6TX52.1	P0C5B9.1
Q1BYS7.1	R4MDK6.1	S5F815.1	W6GWM1.1	P9WFC9.1	P9WFJ9.1	P14916.1	P69996.1
P9WFC5.1	Q8VKQ6.1	P9WHS3.1	A5MKI6.1				

Table 5 - LIST OF ACCESSION NUMBERS FOR FUNGAL ANTIGENS FROM IEDB and UNIPROT

Q5ANA3.1	Q5A3P6.1	Q59VM7.1	Q5A1A9.1	Q5APF0.1	Q8J0P4.1	Q4WHG0.1	Q4WQ87.1
Q59X67.1	Q59Z17.1	Q59ZI3.1	Q5AA33.1	B8N4Q9.1	Q4WAW6.1	Q4WAJ6.1	Q4X1V0.1
A0A1D8PQ86.1	Q59ZB1.1	Q873N2.1	Q59L72.1	B8NIF0.1	P46075.1	Q4WCL1.1	Q4WRP2.1
Q59L12.1	Q59LC9.1	P48989.1	Q5AFC2.1	B8N406.1	Q4WGL5.1	Q9HEQ8.1	Q4WVI6.1
P46593.1	P82611.1	Q5ADV5.1	Q59SG9.1	P41750.1	O00092.1	Q4WEN1.1	Q4WCV3.1
P0DJ06.1	O94038.1	Q59WD3.1	Q59RQ0.1	B8NM71.1	Q4WLW8.1	Q4WI37.1	Q4WNI1.1
P29717.1	P46589.1	Q59W04.1	Q59RK9.1	B8MYS6.1	Q8X176.1	Q4WZS1.1	Q4WQH4.1
Q9UW14.1	Q5AF56.1	Q59VN0.1	P31353.1	B8N8Q9.1	Q96UX3.1	Q4WDA4.1	Q4WDE1.1
Q92207.1	P83773.1	Q59WB9.1	Q5ACM4.1	B8N8R3.1	Q4WPF5.1	Q4WLS7.1	Q4WJT7.1
Q5A8T7.1	Q59YU1.1	Q59P53.1	Q5ACI8.1	B8N417.1	Q92450.1	Q4WWM6.1	Q4WLG1.1
Q5A8T4.1	Q59YV2.1	Q5A432.1	Q5AB93.1	B8N8R0.1	Q4WAW9.1	Q4WP81.1	Q4WQR6.1
P43076.1	Q5ABE5.1	Q5AK64.1	Q5ALL8.1	B8NM74.1	A4GYZ0.1	Q6MYT0.1	Q4WZS2.1
Q5AP53.1	Q59LF2.1	A0A1D8PNZ7.1	Q5A4X8.1	B8N106.1	Q4WAW3.1	Q4WTL0.1	Q4WXP0.1
Q5AL52.1	Q8NJN3.1	Q59Q30.1	Q5AD34.1	B8NHY4.1	Q70J59.1	Q4WXV2.1	Q4WU59.1
P43079.1	Q5ALN1.1	A0A1D8PN12.1	Q59V02.1	B8NJG8.1	Q4X1A4.1	Q4X0Z3.1	Q4WUG4.1
Q5AD07.1	Q59S72.1	Q5AK24.1	Q5AHC0.1	B8NM66.1	E9R876.1	Q4WN25.1	Q4WIK9.1
Q5A0E5.1	Q59K86.1	Q5AFT2.1	Q59Y11.1	B8MYL0.1	M4VQY9.1	Q4WN21.1	Q4WYP0.1
Q5AKU6.1	Q5AGD1.1	Q5A0W6.1	Q59QA5.1	B8NM62.1	Q4WF53.1	Q4X1N0.1	Q4X0B5.1
Q59RL7.1	P79023.1	P0CB63.1	Q5AMJ5.1	B8NGT5.1	Q4WZ64.1	Q4WQV2.1	Q4WYK9.1
G1UB61.1	Q59LP6.1	Q59U11.1	Q5AMF7.1	B8NM64.1	Q4WAZ0.1	Q4WZP2.1	Q4WY33.1
Q5ABC6.1	Q5AP87.1	P83775.1	Q5ABW2.1	B8NV37.1	Q4WR16.1	Q4WVK2.1	Q4X1F8.1
A0A1D8PQB9.1	P22274.1	Q5APF2.1	Q5APJ9.1	B8N151.1	Q4WLB9.1	Q4WUA0.1	Q4WA45.1
P87020.1	Q5AC48.1	Q59VP2.1	Q5AM72.1	B8NEJ3.1	Q4WQS0.1	A4DA84.1	Q4WKD7.1
P0CY27.1	Q5AP59.1	Q5AEE1.1	Q5ACU3.1	B8N8M2.1	Q4WEP7.1	Q4WJX0.1	Q4WCH5.1
Q59XX2.1	Q59MV1.1	Q5AMR5.1	Q5A1V3.1	B8MYV0.1	E9R9Y3.1	Q4WP38.1	Q4WXY3.1
Q59U10.1	Q5AL27.1	Q59SU5.1	Q59RF7.1	B8N7I7.1	P41748.1	Q4X1D7.1	Q4WPL7.1
Q59RW5.1	Q5AJD2.1	Q59VP1.1	Q5ACN3.1	B8NJG3.1	Q4WYG3.1	Q4W9Z9.1	Q4X136.1

Q59MQ0.1	P0CU38.1	Q5ADQ0.1	Q5AHE8.1	B8N8R1.1	P87184.1	Q4WE62.1	Q4WZ44.1
Q5ABU7.1	Q59QC5.1	Q5AK59.1	Q5AHA4.1	B8NJH2.1	Q4WBS1.1	Q4WZL3.1	Q4WTC7.1
Q9Y7F0.1	Q5A5N6.1	Q59RH5.1	Q5AEG7.1	B8NQ51.1	Q70DX9.1	Q4WB37.1	Q4WMK2.1
Q5AC08.1	Q59Q79.1	Q5ACW8.1	Q59V01.1	B8NM63.1	Q4WG16.1	Q4W9Z4.1	Q4WNC9.1
P30575.1	Q5AH38.1	Q5AGM0.1	Q5AK97.1	B8NM73.1	Q96X30.1	Q4WDD0.1	Q4WY67.1
Q5AAG6.1	Q5AMN3.1	Q59VN2.1	Q5A1B2.1	B8NYX0.1	Q4WV19.1	Q4WKB9.1	Q4WU12.1
O74189.1	Q5A1Z5.1	O94069.1	Q5AJK6.1	B8N3P7.1	Q4WAZ6.1	Q4WU07.1	Q4WA61.1
Q59W62.1	Q5A6K2.1	P0CY20.1	Q59L96.1	B8NJH1.1	Q4W944.1	Q4WBL6.1	Q4WA58.1
P0CY34.1	Q59L25.1	Q59XQ1.1	Q59MD0.1	B8MXJ7.1	Q4WTV7.1	Q4WX13.1	Q4WA60.1
Q5A1D3.1	Q5A922.1	O94048.1	Q5AG46.1	B8NJB0.1	Q4WMJ9.1	Q4WV71.1	Q4WX36.1
Q5AJU7.1	Q5AFG1.1	Q5ADX2.1	Q59VW6.1	B8NPS7.1	Q4WZ65.1	Q4X0C2.1	Q4WA62.1
Q5A4H5.1	Q5ALR8.1	P46586.1	Q5A8I6.1	B8N7Z8.1	A0A067Z9B6.1	Q4WRU4.1	Q4WA59.1
Q59Y31.1	Q5AEI2.1	P83776.1	Q9UW24.1	B8NSV5.1	Q66WM4.1	Q4WGS4.1	Q4WXQ7.1
P0CY29.1	Q5AI71.1	Q5A895.1	Q59Q38.1	B8MZA3.1	Q6T267.1	Q4WP13.1	Q4WVA0.1
Q5ANJ4.1	Q5ABA6.1	Q59PP0.1	Q5ADL0.1	B8NLY9.1	Q4WLW5.1	Q4WHG5.1	Q4WDN4.1
Q59NH8.1	Q5ABX0.1	Q5AHH4.1	Q5AH11.1	B8NR69.1	Q4WMJ0.1	Q4WPF7.1	Q4WK03.1
P0CY33.1	Q5A4N0.1	Q96UX5.1	Q59W55.1	B8MZ41.1	Q4WQU0.1	Q4WH83.1	Q4WCG2.1
Q00310.1	Q59TN9.1	P87206.1	Q5AC37.1	B8N7S7.1	Q4WMJ8.1	Q4WXW1.1	Q4WX99.1
Q5A0W9.1	Q5A5S7.1	Q5A029.1	Q5A7Q3.1	B8NR71.1	Q4WWN8.1	Q8NJM2.1	Q4WV10.1
Q5A4M8.1	Q59UG3.1	Q5A1E0.1	Q59PV6.1	A0A0D9MRV9.1	Q4WZ63.1	Q4WWD3.1	Q4WIS6.1
Q5AJC0.1	P0C075.1	Q59XL0.1	P0CH96.1	P55790.1	Q4WVN4.1	Q4WPU8.1	Q4WP65.1
Q59SU1.1	Q59R09.1	Q5A6U1.1	P83782.1	B8NM72.1	Q4WAY8.1	Q4WN99.1	Q4WUK1.1
Q5AG71.1	Q9B8D4.1	Q5A8I8.1	Q5A660.1	B8MW78.1	Q4WY07.1	P0C959.1	Q4WKN3.1
Q5AMT2.1	Q9B8D3.1	Q59PR9.1	Q59YT1.1	Q9P900.1	Q4WZ66.1	Q4X0S7.1	Q4WG58.1
Q59KY8.1	Q9B8D5.1	O74261.1	P53709.1	B8NDE2.1	Q4WQZ5.1	Q4WPW2.1	Q4WXX9.1
Q59LY1.1	Q59LR2.1	Q96VB9.1	Q5ACX1.1	B8NJF4.1	O42630.1	Q4X1U0.1	Q4WC37.1
Q59UT4.1	Q5AED9.1	Q5AQ47.1	Q5ADP9.1	B8NIV9.1	P0C7S9.1	Q4WP57.1	Q4X1Y0.1
Q5ABC5.1	Q5A4W8.1	Q5A985.1	Q92210.1	B8NG16.1	Q4WI46.1	Q4WPH9.1	Q4WZL8.1
Q59MV9.1	Q5ANH2.1	Q59ZW2.1	Q59MA3.1	B8NX60.1	Q4WQY4.1	Q4WDK5.1	Q4WR80.1
Q59MD2.1	Q5A649.1	P83784.1	Q5AFK3.1	B8NM75.1	Q4WAY3.1	Q4WI71.1	Q4WY53.1
Q5A8N2.1	Q5AI22.1	Q59P11.1	Q59S63.1	B8MZZ6.1	Q4WT66.1	Q4WYS7.1	Q4WL88.1
P40953.1	Q5A950.1	Q5ADN8.1	Q5A0Y2.1	B8NM67.1	Q6MY57.1	Q4WY08.1	Q4WGV9.1
Q5APR8.1	Q5ANC9.1	Q5A849.1	Q5ALW7.1	B8NRX2.1	P0C954.1	Q4WND3.1	Q4WC29.1
P10613.1	Q59UH7.1	Q5A7R7.1	Q59W52.1	B8NXJ2.1	Q4W946.1	Q4X1D2.1	Q4WKV8.1
Q5A5Q6.1	Q5ALX8.1	Q59XB0.1	Q59S42.1	B8NMD3.1	Q4WMJ5.1	Q6MY91.1	Q4WYA5.1
Q5A4F3.1	Q5AI37.1	Q59P96.1	Q5A961.1	B8NBI2.1	Q70GH4.1	Q4WRV2.1	Q4WCM6.1
P43094.1	Q5ABV4.1	Q59SR6.1	Q59ST6.1	B8NPA4.1	Q4WUL6.1	Q4WRX4.1	Q4WKB2.1
Q9P940.1	Q5AKU4.1	Q9P975.1	Q59N74.1	B8N803.1	P61832.1	Q4WP03.1	Q4WNG7.1
Q5AJY5.1	Q59VY1.1	O94083.1	Q5A6P6.1	B8NPT0.1	Q4WG11.1	Q4WTA6.1	Q4WRE8.1
P39827.1	Q59Z51.1	Q5AIA4.1	Q59XM0.1	B8MXP5.1	Q4WYU4.1	Q4WZJ0.1	Q9P8P4.1
Q59WF4.1	Q59LV8.1	Q59YF4.1	Q5A4N5.1	B8NIB8.1	Q4WYR6.1	Q4W9S8.1	Q4WJS4.1
P83774.1	Q59X11.1	Q59XW9.1	Q5A6M2.1	B8N9H4.1	Q4WNE1.1	Q4X054.1	Q4WHW1.1
Q59Q46.1	Q5ABQ7.1	Q59WU8.1	Q5A5M7.1	B8NNK9.1	Q4WQZ6.1	Q4X1I3.1	Q4WYG7.1
Q59X23.1	Q59PZ3.1	Q5AAR0.1	Q5A6N8.1	B8NI03.1	Q4WWC6.1	Q4W9V1.1	Q4WJH4.1
P46614.1	O13332.1	Q5AQ62.1	Q9UVJ4.1	B8NM76.1	Q6Q487.1	Q4WDF1.1	Q4WJM6.1
Q5AQ33.1	Q5AHD6.1	Q59R35.1	Q59V88.1	B8NM79.1	P0C957.1	Q4WWN2.1	Q4WMB6.1
P82610.1	A0A1D8PPG4.1	Q5A847.1	Q59RA0.1	B8NJG9.1	Q4WM08.1	Q4WTH0.1	Q4WMU9.1
Q5AP80.1	Q5ADW3.1	Q5A6A4.1	Q59XU5.1	B8NPL7.1	Q4W9B8.1	Q4WJQ1.1	Q4WIF3.1
P46598.1	Q5AML6.1	Q5A4Q1.1	Q5AH12.1	B8NMR5.1	Q4WWJ1.1	Q4WKL7.1	Q4WEH7.1
Q5A506.1	Q5A846.1	P0CY22.1	Q59ZX3.1	B8NP65.1	E9RCR4.1	Q4WX90.1	Q4WT34.1
Q5A599.1	A0A1D8PPI5.1	P42800.1	Q5AB48.1	B8N5S6.1	Q4WM67.1	Q4WG69.1	Q4WT99.1
Q59NP5.1	P0CT51.1	Q59KI4.1	Q5A3Q0.1	B8NJ86.1	Q4WUN7.1	Q4WM32.1	Q4X0N1.1
Q5AHA0.1	Q59MA6.1	Q59JU3.1	Q5A6M0.1	P41747.1	E9QRF2.1	Q4WTI3.1	Q4WSA8.1
Q07730.1	Q5ALW2.1	P83777.1	Q5AL29.1	P41765.1	Q4WK60.1	Q4WHX4.1	Q4WLD1.1
Q5AD05.1	Q5ABU8.1	Q5A310.1	Q59KG2.1	B8N6V7.1	Q4WZ61.1	Q4WXE9.1	Q4WMU5.1
Q5AME2.1	Q5AEC6.1	Q59N80.1	O42825.1	B8NKE9.1	Q4W945.1	Q4X0X6.1	O13410.1
P41797.1	Q5A4X0.1	Q5AJ77.1	O59931.1	B8NGU6.1	Q4WMA6.1	Q4W8Z9.1	Q4WG40.1
P0CY24.1	Q59LX9.1	Q59ZV4.1	Q5AM44.1	B8NBP9.1	Q4WNS8.1	Q4WEB4.1	Q4WLD5.1
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Q5ABE2.1	Q5ACL9.1	Q59L13.1	Q5AK94.1	B8NKI4.1	Q4WUR1.1	Q4X1N4.1	Q4WLD2.1
Q59M56.1	Q5ABT8.1	Q5AG97.1	Q5AKB1.1	B8NQQ7.1	Q4WQ08.1	Q4WMP0.1	Q4WLC9.1

Q5AK51.1	Q5AMH3.1	Q5AB15.1	Q59VM4.1	B8NJH0.1	Q4WF61.1	A4D9B6.1	Q4WQ54.1
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Q5AAF4.1	Q5AJC1.1	Q59KN8.1	Q5AJ92.1	B8NM78.1	Q4WQZ3.1	Q4WM95.1	Q4X161.1
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Q5ADT1.1	Q5AGC7.1	Q5AFP8.1	Q5ABP8.1	B8MWJ5.1	Q4WNV0.1	Q4WLV6.1	Q4WQ14.1
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P46587.1	P78599.1	Q5APM7.1	Q59KF3.1	B8N5T6.1	Q4WCZ8.1	Q4WJW8.1	Q4WYJ7.1
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Q5A7S7.1	Q5AAG1.1	Q9B8C9.1	Q5A302.1	B8MWR8.1	Q4WRB0.1	Q4WCL1.1	Q4WQZ1.1
P28870.1	Q59YL9.1	Q9B8D2.1	Q5AH60.1	B8N4G0.1	Q4WC55.1	Q9HEQ8.1	Q4WQY7.1
Q59NX5.1	Q59PL9.1	Q9B8D1.1	Q5A692.1	B8N9M5.1	Q4WMV5.1	Q4WEN1.1	Q4WQY5.1
Q5ABG1.1	Q59QL0.1	Q59M69.1	Q59Q39.1	Q00278.1	Q4WAZ2.1	Q4WI37.1	Q4WXT2.1
Q5AP52.1	Q5A1U8.1	Q59VX9.1	Q59NW5.1	B8NPX1.1	Q92197.1	Q4WZS1.1	Q8J130.1
P0CY31.1	O74198.1	Q59YD8.1	Q5A6Q4.1	B8NYW8.1	Q4WSE8.1	Q4WDA4.1	Q4WJX5.1
P13649.1	Q5A013.1	Q59QH0.1	P43075.1	B8N219.1	Q4WX94.1	Q4WLS7.1	Q4X1I8.1
Q5AG77.1	P87163.1	Q5A8A2.1	Q59Q36.1	B8NQK0.1	Q4WLD0.1	Q4WWM6.1	Q4WVW4.1

Q9UW13.1	Q5AI86.1	Q9B8D7.1	Q92410.1	Q12732.1	Q4WUK5.1	Q4WP81.1	Q4WTH1.1
P0CU34.1	Q5AM80.1	Q9UW25.1	Q5A1M4.1	Q9HEY7.1	Q8TGG5.1	Q6MYT0.1	Q4WLI9.1
P40954.1	Q5A6Q7.1	Q59XY9.1	Q5ANC8.1	Q6UEG8.1	Q4WTK9.1	Q4WTL0.1	Q4WQJ5.1
Q04802.1	Q5AGV4.1	Q5A2T0.1	Q5A4K7.1	O42716.1	Q4WVU5.1	Q4WXV2.1	Q4WQJ2.1
P0CY35.1	Q5AJ82.1	Q5AGW8.1	Q5ADL8.1	Q9UW95.1	Q4WLM7.1	Q4X0Z3.1	Q4WK56.1
Q5AAU5.1	Q5AIA1.1	Q5ADS3.1	Q59RQ2.1	Q9Y8D9.1	Q4W9P4.1	Q4WN25.1	Q4WJS2.1
Q59VQ8.1	Q5A9Z6.1	Q5ACR4.1	Q5APC0.1	A2SZW8.1	Q4WIT0.1	Q4WN21.1	Q4WJT9.1
Q59VF4.1	Q5AGC1.1	P0CU36.1	Q5A931.1	Q2U2U3.1	Q4WQB9.1	Q4X1N0.1	Q4WUV8.1
Q5A0X8.1	Q59ZV5.1	Q5A2Y7.1	Q59VW7.1	Q00258.1	Q4WGK6.1	Q4WQV2.1	Q4WX68.1
O13426.1	Q59VP7.1	Q5A368.1	Q5AKU5.1	Q12437.1	Q4WMR0.1	Q4WZP2.1	Q4WHN8.1
Q5A0M4.1	Q5A7P3.1	Q9B8D6.1	Q59MN0.1	E9QYP0.1	Q4WYE5.1	Q4WVK2.1	Q4WJU8.1
Q59PF9.1	Q5A6K8.1	Q9B8D0.1	Q59WH7.1	Q4WS76.1	Q4WZ01.1	Q4WUA0.1	Q4WBT4.1
Q5AFP3.1	Q5AD13.1	Q5A2K0.1	Q96WL3.1	Q4WMJ7.1	Q4W930.1	A4DA84.1	Q4WZV6.1
Q5AEK8.1	Q04782.1	Q5A1Q5.1	Q59ZX6.1	P28296.1	Q4WBR0.1	Q4WJX0.1	Q4WUV9.1
Q5AFK0.1	Q5A0J9.1	Q5AEM5.1	Q59MU1.1	E9RAH5.1	Q4WHD1.1	Q4WP38.1	Q4WLV2.1
Q5APD4.1	Q59ZZ6.1	Q5AK25.1	Q5A0J0.1	Q4WW81.1	Q4WTB3.1	Q4X1D7.1	Q4WFS2.1
Q5ADQ9.1	Q5AH25.1	Q5AK10.1	Q59WK2.1	Q50EL0.1	Q4WRV9.1	Q4W9Z9.1	Q4WBM1.1
P83779.1	Q59XM1.1	Q5AI15.1	P43073.1	Q4WY82.1	Q4X267.1	Q4WE62.1	Q4WAU7.1
Q5AAH2.1	Q59NN8.1	Q5AEM8.1	P87220.1	Q4WSF6.1	Q4WVZ3.1	Q4WZL3.1	Q4WZS3.1
O74254.1	Q5AP65.1	Q5A4J4.1	Q5ABD9.1	E9RCK4.1	Q4WR24.1	Q4WB37.1	Q4WPU9.1
Q5AL49.1	Q5AFF7.1	Q59YK4.1	P83781.1	Q4WZA8.1	Q4WPM8.1	Q4W9Z4.1	Q4WVZ0.1
P53697.1	Q59VR3.1	Q59WV0.1	Q5ANB1.1	Q4WAW7.1	Q4WE86.1	Q4WDD0.1	Q4WCX9.1
Q5ACL7.1	Q5AFH3.1	Q5AHB1.1	Q5A0E2.1	Q92405.1	A4DA70.1	Q4WKB9.1	Q4WJ38.1
Q5AEM6.1	P83780.1	Q5APK0.1	Q5AMG5.1	Q4WRY5.1	Q4WW45.1	Q4WU07.1	Q4WRC2.1
Q8TG40.1	Q5A4G9.1	Q59PW0.1	Q5A6T8.1	Q7Z7W6.1	Q4WVG2.1	Q4WBL6.1	Q4WWW5.1
Q59X38.1	Q59NQ9.1	O74711.1	Q59WG5.1	Q4WZ67.1	Q4WQG9.1	Q4WX13.1	Q4WC84.1
Q59VQ3.1	A0A1D8PNP3.1	Q5ADN9.1	Q5AI80.1	Q4WZB3.1	Q4WQN1.1	Q4WV71.1	Q4WTW3.1
Q5A7Q2.1	Q5A9Z1.1	Q5ACP5.1	Q5AB49.1	Q4WLN1.1	Q4WCF1.1	Q4X0C2.1	Q4WFV6.1
Q5AJV5.1	A0A1D8PK89.1	Q5A1E1.1	Q59R32.1	Q4WR82.1	Q4WZC3.1	Q4WRU4.1	Q4WKD9.1
Q5A3Z6.1	Q59WB3.1	Q59L86.1	Q5A061.1	O14434.1	Q4WYX7.1	Q4WGS4.1	Q4WP10.1
Q5A201.1	Q59ZC8.1	Q5AD23.1	Q59P50.1	Q4WMK0.1	Q4X0A5.1	Q4WP13.1	C5JZM2.1
O93827.1	Q5A1L6.1	Q5A5U6.1	Q59WC6.1	Q4WPX2.1	Q4WUD3.1	Q4WHG5.1	P0DJ06.1
Q5AAI8.1	A0A1D8PN14.1	Q5ADQ7.1	Q5AI48.1	O43099.1	Q4WS49.1	Q4WPF7.1	P46598.1
Q5A2J7.1	Q5A8X7.1	Q59WJ4.1	Q59ZU1.1	Q4WJ81.1	Q4WCX7.1	Q4WH83.1	P87020.1
P22011.1	Q59X39.1	Q5AGV7.1	Q5AG56.1	P67875.1	Q4WXX5.1	Q4WXW1.1	P38110.1
Q9HGT6.1	Q5ACW6.1	Q59NR8.1	Q59T36.1	Q4WZB4.1	Q4WNB5.1	Q8NJM2.1	C1GK29.1
Q9UW26.1	P0CB54.1	Q5A5K7.1	Q9P840.1	E9QUT3.1	O42799.1	Q4WWD3.1	
Q59LX5.1	A0A1D8PN88.1	Q5A210.1	Q5AHB8.1	Q4WAZ9.1	Q4WHA3.1	Q4WPU8.1	
Q59PT0.1	A0A1D8PMB1.1	Q59N10.1	Q5AKU3.1	Q4WZ70.1	Q4W9M3.1	Q4WN99.1	
Q3MNT0.1	Q5ABR2.1	Q5A1B3.1	Q59ZW4.1	E9RBR0.1	Q4WVH5.1	P0C959.1	

Table 6 - LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

	P19594.1	P28335.1	P29000.1	M5ECN9.1	P38948.1	P00709.1	P79085.1
P49148.1	Q6R4B4.1	P42037.1	Q9HDT3.1	P42058.1	P0C0Y4.1	P27759.1	Q2KN25.1
P00304.1	Q2KN24.1	Q2KN27.1	P43174.1	P10414.1	Q8L5L5.1	Q8GZP6.1	Q8H2B8.1
Q7Z1K3.1	A1IKL2.1	Q7M1X6.1	P49372.1	P00630.1	P43238.1	Q45W87.1	Q6PSU2.1
O82580.1	Q647G9.1	Q9SQH1.1	C7E3T4.1	H6VGI3.1	Q84ZX5.1	A0PJ16.1	P67875.1
P40292.1	P28296.1	P79017.1	Q96X30.1	Q4WWX5.1	O60024.1	Q92450.1	Q09072.1
Q09097.1	P04403.1	P15494.1	P25816.1	P43187.1	Q39419.1	O65002.1	P05814.1
P13916.1	Q9UAM5.1	P54958.1	D0VNY7.1	P54962.1	O18598.1	Q1A7B3.1	Q9NG56.1
A0ERA8.1	Q8MUF6.1	A7IZE9.1	O96870.1	P02663.1	P02666.1	P02668.1	Q28133.1
P00711.1	P02754.1	P02769.1	P02662.1	O18873.1	P49822.1	P09582.1	B5KVH4.1
Q14790.1	E9R5X9.1	Q96385.1	Q7M1E7.1	P02229.1	Q7XCK6.1	P40108.1	P42039.1
P42040.1	P42059.1	P0C0Y5.1	P02465.1	Q6IQX2.1	P20023.1	Q08407.1	Q8S4P9.1
Q9ATH2.1	Q8W1C2.1	P18632.1	P43212.1	Q9SCG9.1	Q9M4S6.1	Q69CS2.1	Q96VP3.1
O04701.1	O04725.1	P94092.1	P04800.1	Q7M1X8.1	Q41183.1	P93124.1	P82946.1
O04298.1	Q58A71.1	Q23939.1	Q967Z0.1	Q1M2P5.1	Q94507.1	Q8MVU3.1	Q86R84.1

Q00855.1	P49275.1	Q26456.1	P08176.1	Q8N0N0.1	P49278.1	Q2L7C5.1	P39675.1
Q9Y197.1	P14004.1	P49273.1	Q7Z163.1	Q9UL01.1	O15315.1	P11388.1	P30575.1
Q95182.1	P41091.1	O15371.1	P25780.1	Q2PS07.1	P49327.1	P30438.1	Q5VFH6.1
Q7XAV4.1	P04075.1	Q90YL0.1	P01005.1	P01012.1	P19121.1	P02230.1	P02224.1
P02227.1	Q9NJQ6.1	O65809.1	P26987.1	P04776.1	P04347.1	P04405.1	P08238.1
P12031.1	P15252.1	Q7Y1X1.1	P52407.1	O82803.1	Q39967.1	P02877.1	P62805.1
P43216.1	O23972.1	P24337.1	Q7Y1C1.1	P93198.1	Q9SEW4.1	Q2TPW5.1	P81294.1
P81295.1	O64943.1	P07498.1	Q84UI1.1	P80384.1	P31025.1	Q004B5.1	P14946.1
Q7M1X5.1	P14947.1	P14948.1	Q5TIW3.1	Q40237.1	P14174.1	Q5H786.1	P30440.1
P11589.1	P43211.1	P40967.1	Q01726.1	Q16655.1	Q07932.1	Q9ZNZ4.1	Q9H009.1
P12036.1	Q15233.1	Q5RZZ3.1	Q8GZB0.1	Q8NFH4.1	P19963.1	Q94G86.1	P01014.1
P22895.1	P43217.1	P55958.1	B8PYF3.1	O75475.1	O24554.1	Q0IX90.1	Q52PJ2.1
K7VAC2.1	Q3Y8M6.1	Q9URR2.1	Q9P8G3.1	A1KYZ2.1	P23284.1	Q9TZR6.1	Q25641.1
P00433.1	Q41260.1	P56164.1	Q40967.1	Q8H6L7.1	P35079.1	Q9XG86.1	P43214.1
Q5ZQK5.1	Q40960.1	P43215.1	O82040.1	Q8L5D8.1	P82242.1	Q9HCM2.1	Q9ZP03.1
Q9FPR0.1	B6T2Z8.1	Q9C5M8.1	P15722.1	P25788.1	P81651.1	O24248.1	P82534.1
E3SH28.1	O65457.1	B6RQS1.1	P02761.1	P67876.1	Q9Y4W2.1	Q9ULX3.1	P83181.1
Q8L5K9.1	C1KEU0.1	Q91482.1	Q9XHP1.1	P15322.1	Q15020.1	B9SA35.1	P01267.1
O00267.1	D2T2K3.1	Q9T0P1.1	Q07283.1	Q7M3Y8.1	P25445.1	Q5NT95.1	P07101.1
O15205.1	O00762.1	D2KFG9.1	H9AXB3.1	Q8W3V4.1	P49370.1	Q05110.1	Q9ULJ6.1
Q2VST0.1	ABL09307.1	ABL09312.1	AGC39172.1	AGC39173.1	AGC39174.1	P00785.4	P85204.1
AGC39168.1	CAM31908.1	ABB77213.1	P83958.1	AGC39176.1	CAA34486.1	AAA32629.1	A5HII1.1
CAM31909.1	P85206.1	P86137.2	P85524.1	CAI38795.2	ABQ42566.1	AAR92223.1	P84527.1
AGC39164.1	AGC39165.1	AGC39166.1	AGC39167.1	4X9U_B	AGC39169.1	AGC39170.1	AGC39171.1
AAC37218.1	P50635.2	XP_001657556.2	P18153.2	AAB58417.1	ABF18122.1	XP_001653462.1	XP_001654143.1
XP_001654291.1	ABF18258.1	XP_001655948.1	XP_001655954.1	P13080.1	E37396	Q7M1X7	Q7M1X9
AAB24432.1	CAA76831.1	AAB47552.1	AAM77471.1	AAS75297.1	3V0R_A	4AUD_B	CAA55071.2
P49148.1	Q6R4B4.1	P78983.2	Q00002.2	AAB48041.1	P42037.1	Q9HDT3.2	P42058.1
OWY50380.1	AAO91800.1	P0C0Y4.2	AGS80276.1	CAD38167.1	ABI26088.1	ACP43298.1	AKV72168.1
P27759.1	P27760.1	P27761.1	P28744.1	AAA32669.1	CBW30986.1	CBW30987.1	CBW30988.1
CBW30989.1	CBW30990.1	CBW30991.1	CBW30992.1	CBW30993.1	CBW30994.1	CBW30995.1	AAX77686.1
P27762.1	CBJ24286.1	CBK52317.1	CBK62693.1	CBK62694.1	CBK62695.1	CBK62697.1	CBK62698.1
CBK62699.1	O04004.1	AAP15203.1	AAP15202.1	AAP15201.1	AAX77687.1	AAX77688.1	5EM1_A
5EV0_B	AAX77684.1	AAX77685.1	AHA56102.1	5EGW_B	P00304.2	P02878.1	AAA20065.1
AAA20067.1	AAA20064.1	AAA20066.1	AAA20068.1	P10414.2	AEK65120.1	AAM73729.1	AAM73730.2
AAN76862.1	AAL91665.1	O23791.1	Q94JN2.1	CDZ09832.1	AGC60026.1	AGC60027.1	AGC60028.1
AGC60020.1	Q7Z1K3.1	AGC60035.1	AGC60036.1	ACZ95445.1	BAJ78220.1	BAJ78221.1	BAJ78222.1
BAJ78223.1	AGC60029.1	AGC60030.1	AGC60031.1	BAT62430.1	AAF75225.1	Q9NJA9.1	Q9NAS5.1
AEQ28167.1	P83885.1	CAK50389.1	BAF43534.1	ABL77410.1	BAF75681.1	BAF75704.1	BAF75705.1
BAF75706.1	BAF75707.1	BAF75708.1	BAF75709.1	BAF75710.1	BAF75711.1	BAF75712.1	ABV55106.1
CAB58171.1	G37396	Q7M1X6	Q7M1Y0	A59055	AAK09361.1	Q7M4I5.1	P01502.1
P00630.3	ABF21077.1	ABF21078.1	Q08169.1	ACI25605.1	Q5BLY5.1	CAA26038.1	MEHB2
NP_001119715.1	NP_001035360.1	ABD51779.1	NP_001011564.1	AAY21180.1	CAD56944.1	AHM25038.1	AHM25037.1
AHM25036.1	AHM25035.1	P49372.1	P92918.1	ACV04796.1	AAD29409.1	P81943.3	P86809.1
AAB22817.1	P43237.1	P43238.1	AAT00595.1	AAT00594.1	AAT00596.1	ADQ53858.1	3SMH_A
3S7E_A	B3EWP3.1	C0HJZ1.1	B3EWP4.1	AAN77576.1	AAM78596.1	AAK96887.1	ACN62248.1
AAC63045.1	AAD47382.1	AAM46958.1	AAM93157.1	ABI17154.1	ACH91862.1	3C3V_A	ADQ53859.1
AAD55587.1	ADB96066.1	AGA84056.1	AAD56337.1	AAL37561.1	1W2Q_A	Q647G9.1	AAD56719.1
ABW17159.1	AAQ91847.1	ABP97433.1	ACA79908.1	ABG85155.1	ABX56711.1	ABX75045.1	AAU21499.2
AAU21500.1	AAZ20276.1	Q45W86	CAG26895.1	2X45_A	AHF71021.1	AHF71022.1	AHF71023.1
AHF71024.1	AHF71025.1	AHF71026.1	AAO24900.1	CAK50834.1	P0C088.1	ACE07186.1	ACE07187.1
ACE07188.1	ACE07189.1	CAD12861.1	CAD12862.1	5EM0_A	AAX85388.1	AAX85389.1	CAD23611.1
CAD23613.1	CAD23614.1	BAH09387.1	AAD13644.1	AAD13645.1	AAD13647.1	AAD13649.1	AAD13650.1
AAD13651.1	AAD13652.1	AAB93837.1	AAB93839.1	AAD13646.1	ACN32322.1	AAB26195.1	Q06811.2
2XV9_A	P46436.3	Q9UVU3	CAA06305.1	AAF86369.1	P67875.1	CAA59419.1	CAB44442.1
CAA73782.1	AAB07620.1	P79017.2	AAK49451.1	Q96X30.3	AAM43909.1	Q8NKF4.2	CAI78448.1
CAI78449.1	CAI78450.1	AAB95638.1	CAM54066.1	CAA04959.1	O60024.2	CAA83015.1	P46075.3
AAB60779.1	Q92450.3	O42799.2	CAB64688.1	Q9UUZ6.2	CAA11266.1	Q875I9.1	EAL89830.1

Q4WB37.1	KEY81716.1	KEY78748.1	AAA32702.1	CAB06417.1	AAD13106.1	P0C1B3.1	AAA32708.1
P12547.2	ADE74975.1	P29600.1	P00780.1	AAG31026.1	BAA05540.1	BAF46896.1	AIV43661.1
BAH10149.1	P04403.2	AAO38859.1	A45786	CAA54696.1	CAA54695.1	CAA54694.1	CAA96546.1
CAA96539.1	CAA96540.1	CAA96541.1	CAA96542.1	CAA96543.1	CAA96544.1	CAA96547.1	P43186.2
CAB02155.1	CAB02156.1	CAB02157.1	CAB02158.1	CAB02159.1	CAB02160.1	CAB02161.1	CAA96545.1
CAA05186.1	CAA05187.1	CAA05188.1	CAA05190.1	CAA07318.1	CAA07319.1	CAA07323.1	CAA07324.1
CAA07325.1	CAA07326.1	CAA07327.1	CAA07329.1	CAA07330.1	CAA04823.1	CAA04826.1	CAA04827.1
CAA04828.1	CAA04829.1	AAD26560.1	AAD26561.1	AAD26562.1	P43180.2	1QMR_A	AAP37482.1
1LLT_A	AAB20452.1	CAA07328.1	CAA07320.1	CAA54488.1	1B6F_A	4BK7_A	4B9R_A
4BKC_A	4BKD_A	4BK6_B	CAA33887.1	CAA54482.1	CAA54483.1	CAA54484.1	CAA54487.1
CAA54489.1	CAA54421.1	CAA54481.1	4BTZ_A	4Z3L_D	B45786	1CQA_A	AAA16522.1
A4K9Z8.1	CAA55854.1	CAA60628.1	AAG22740.1	CAC84116.1	AHF71027.1	BAB21489.1	BAB21490.1
BAB21491.1	AAB25850.1	AAB25851.1	AJO53282.1	AAB29344.1	AAB29345.1	ACM24358.1	ABC86902.1
AAD13531.1	AAD13530.2	ABC68516.1	1YG9_A	ABP35603.1	AAA86744.1	3LIZ_A	ACY40650.1
ACY40651.1	AAA87851.1	ABP04043.1	ACJ37389.1	ACF53836.1	ACF53837.1	ABP04044.1	AAB72147.1
ABB89296.1	ABB89297.1	ABB89298.1	AAF72534.1	ABX57814.1	AAK58415.1	AAQ24541.1	ABU97466.1
AAM83103.1	AAA78904.1	2MFK_A	AAC80579.1	ABH06350.1	ABH06347.1	ABH06346.1	ABH06348.1
AAX34047.1	AAM10779.1	AAQ24542.1	AAQ24543.1	AAD10850.1	ABH06352.1	ABH06359.1	2JMH_A
APU87558.1	APU87557.1	APU87556.1	APU87554.1	AAQ24545.1	ASX95438.1	AAP35069.1	ACV04860.1
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CAA76556.1	CAA76557.1	CAA76558.1	1NLX_N	CAA76887.1	3FT1_A	AGT28425.1	CAD10390.1
AHC94918.1	CEJ95862.1	CTQ87571.1	ABU42022.1	ABG73109.1	ABG73110.1	ABG73108.1	ABO36677.1
ABR29644.1	CAF25233.1	CAF25232.1	CAB82855.1	AJG44053.1	A0A158V755.1	A0A158V976.1	2N81_A
CAC41633.1	CAC41634.1	CAC41635.1	CAD80019.1	ABY21305.1	ABY21306.1	ALF39466.1	ALF00099.1
CAD20556.1	CAE52833.1	CAC85911.1	CBW45298.1	A60372	F37396	CAA10520.1	AAG42254.1
P22284.1	P22286.1	A60373	P22285.1	AAA29793.1	AAD52615.1	AAD52616.1	AAT95010.1
AAS67044.1	AAS67043.1	AAS67042.1	AAS67041.1	AAP37412.1	AAT95009.1	P35780.1	P83377.1
P83542.1	A2VBC4.1	ADT89774.1	ADL09135.1	P86687.1	ADD63684.1	P86686.1	Q7Z156.2
P05946.1	AGE44125.1	ABL89183.1	ABS12234.1	AFA45339.1	ACN87223.1	AKV72167.1	AHY24177.1
BAH59276.1	AAB97141.1	ADR66945.1	ADR66946.1	ADR66947.1	ADR66948.1	AAC02632.1	AAS47037.1
AAS47036.1	AAS47035.1	1H2O_A	AAF26449.1	ADR66943.1	ADR66944.1	AAD29411.1	AAB38064.1
P82534.1	ACE80974.1	AAL91662.1	3EHK_A	AGR27935.1	ADN39440.1	ADN39441.1	P82952.1
ACE80939.1	ACE80956.1	ACE80958.1	ACE80957.1	ACE80959.1	ACE80955.1	ACE80972.1	P83332.1
P83335.1	AEV57471.1	ABB78006.1	AJE61291.1	AJE61290.1	P81402.1	AAV40850.1	ADR66939.1
AGW21344.1	CAD37201.1	CAD37202.1	P86888.1	BAH10154.1	C0HKC0.1	AHB19227.1	AHB19226.1
AHB19225.1	AAF26451.1	AET05733.1	AET05732.1	AET05730.1	O65200.1	AAD29410.1	AAC24001.1
ABZ81045.1	ABZ81047.1	ABZ81046.1	CAC83046.1	CAC95152.1	CAC83047.1	CAC95153.1	P02761.1

Q63213	AAA41198.1	AIS82657.1	AAP30720.1	AAT37679.1	CAA38097.1	ABG54495.1	ABG54494.1
Q91483.3	ACI68103.1	CAA66403.1	CBL79146.1	ACH70931.1	CBL79147.1	NP_001133181.1	AHL24657.1
ARS33724.1	AAT99258.1	AAX11261.1	AAX11262.1	ACO34813.1	P83181.1	ACO34814.1	ACS34771.1
AHL24658.1	ADK22841.1	ADK22842.1	CAX32966.1	CAX32967.1	SHD75397.1	AAO15613.1	AAS93669.1
AAS93674.1	AAS93675.1	AAS93676.1	AAO15607.1	AAX37321.1	AGM48615.1	CAQ68366.1	BAH10151.1
Q7M1Y1	C37396	D37396	AAP06493.1	AAC67308.1	XP_003030591.1	BAW32538.1	BAW32537.1
BAW32536.1	BAW32535.1	BAC66618.1	CAX32965.1	AFA45340.1	AFJ80778.1	ABS12233.1	CAQ72968.1
CAQ72969.1	AAB37403.1	AAB37406.1	AAB34365.1	CAH92630.1	CAH92627.1	Q7M263	CBG76811.1
BAE54429.1	BAE54430.1	ACB55491.1	AAK15088.1	ACI41244.1	AAD42943.1	AAK15089.1	AAG23840.1
ACH85188.1	AAD42942.1	AAD42944.1	AAK15087.1	CAA62909.1	CAA62910.1	CAA62911.1	CAA62912.1
CAA62908.1	P15322.2	AAX77383.1	AAX77384.1	ABU95411.1	ABU95412.1	ABU53681.1	NP_001306883.1
NP_001316123.1	CAD10377.1	AAL29690.1	AAL75449.1	AAL75450.1	CAJ19705.1	AAB42069.1	CAA75803.1
AHC08074.1	AHC08073.1	ABA81885.1	ABB16985.1	CAA31575.1	CAA27571.1	CAA27588.1	AAA33819.1
P15476.2	P16348.1	P20347.3	AAB63099.1	BAA04149.1	BAH10156.1	AAF65312.1	AAF65313.1
AAC97370.1	AAC97369.1	AAB36117.1	AAB36119.1	AAB36120.1	AAB36121.1	AAT95008.1	P35775.1
AAB65434.1	P35776.2	P35779.2	ADD74392.1	AIL01319.1	AIL01318.1	AIL01316.1	AIL01317.1
AIL01320.1	AIL01321.1	ACT37324.1	1ESF_B	CAJ43561.1	P34071.1	P20723.1	P06886.1
AAT66567.1	ABS29033.1	AAT66566.1	AAD46493.1	AAS75831.1	P00791.3	AAA30988.1	NP_001005208.1
P58171.1	S43242	S43243	S43244	ADX78255.1	ADM18346.1	ADM18345.1	ADK47876.1
P86360.1	CEE03319.1	CEE03318.1	AAK63089.1	AAK63088.1	CBL79145.1	P86978.1	CAX62602.1
P86979.1	BAE54431.1	BAE46763.1	BAH10155.1	AAF07903.2	AAD52013.1	AAD52012.1	Q8J077.1
CAD23374.1	P24296.2	CAA42453.1	ACG59281.1	AKJ77988.1	AKJ77986.1	AKJ77987.1	CAI64398.1
AKJ77990.1	AKJ77985.1	CAA35238.1	CAA25593.1	CAA26383.1	CAA26384.1	CAA26385.1	AAA34275.1
AAA34276.1	AAA34279.1	AAA34280.1	AAA34281.1	AAA34282.1	AAA34283.1	AAA34284.1	BAA12318.1
P81496.1	ACE82289.1	BAE20328.1	CAR82265.1	CAR82266.1	CAR82267.1	BAN29067.1	CAI64397.1
CAI64396.1	P08819.2	P27357.1	ACE82291.1	CAA61945.2	CAA61943.2	CAA61944.2	CAQ57979.1
CBA13560.1	AAA34272.1	AAA34274.1	AAA34288.1	AAA34289.1	BAA11251.1	CAI78902.1	BAN29066.1
CAY54134.1	CAB96931.1	CAA43331.1	CAA31396.1	CAA26847.1	CAA24934.1	CAA43361.1	AAB02788.1
CAA27052.1	CAA24933.1	BAN29068.1	CAA31395.4	AAZ23584.1	BAC76688.1	CAI84642.1	CAA35598.1
CAZ76052.1	CBA13559.1	CAA35597.1	CAC14917.1	ACE82290.1	Q6W8Q2.1	CAA72273.1	CAB52710.1
CAZ76054.1	CAA31685.1	CAA30570.1	AAA34285.1	AAA34286.1	AAA34287.1	O22116	CAA59338.1
CAA59339.1	CAA59340.1	O22108	CAI79052.1	AEH31546.1	BAN29069.1	CAA65313.1	ABS58503.1
P82977.2	CCK33471.1	APY24042.1	CAA34709.1	CAA39099.1	CAA36063.1	CAA44473.1	AAA34290.1
AAX34057.1	AAX34058.1	AAX34059.1	AOD75395.1	AOD75396.1	AOD75399.1	ABQ96644.1	ABU97479.1
AAT40866.1	AAU11502.1	ABM53751.1	ABU97480.1	CAA73221.1	ACL36923.1	ABZ81991.1	AGG10560.1
AAT66607.1	AAT66609.1	ACH42744.1	AAT66610.1	ACJ65836.1	AGC36415.1	ACH42743.1	ACI44002.1
ABQ59259.1	ABQ59258.1	ABQ59255.1	ACJ54737.1	ACH42741.1	AGC36416.1	AKV72166.1	AIV43662.1
BAH10157.1	P0DMB5.1	P0DMB4.1	P0CH87.1	P35781.1	P35782.1	CBY83816.1	CBY93636.1
P81657.1	P35783.1	CAJ28931.1	P35784.1	CAJ28930.1	CAL59818.1	CAL59819.1	P51528.1
P35760.1	ABC73068.1	P0CH89.1	P35785.1	P35786.1	P0CH86.1	P35787.1	AAB48072.1
AAA30333.1	CAB42887.1	1QNX_A	P49370.1	CAI77218.1	2ATM_A	ACA00159.1	AAX19889.1
ABG02262.1	ABW23574.1	BAA74451.1	CAA50008.1	P80273.2	P80274.1	P33556.1	CAR48256.1
ABD79096.1	ABD79097.1	ABD79098.1	ACX37090.1	P29022.1	2209273A	AAO45607.1	AAO45608.1
AAK56124.1	2HCZ_X	ABD79094.1	ABD79095.1	ABF81661.1	ABF81662.1	Q1ZYQ8.2	P0C1Y5.1
AAB86960.1	ABG81312.1	ABG81313.1	ABG81314.1	ABG81315.1	ABG81316.1	ABG81317.1	ABG81318.1
CAA51718.1	CAA51719.1	CAA51720.1	AAG35601.1	5FEF_A	AAA33493.1	AAA33494.1	CAI64400.1
AAX40948.1							

Table 7 -LIST OF ACCESSION NUMBERS FOR AUTOMIMMUNE ANTIGENS FROM IEDB

	I7HKY1.1	Q9P0J1.1	P61604.1	Q9NUQ2.1	Q9P212.1	P16885.1	P09543.1
P17980.1	Q99460.1	O00231.1	O00487.1	P48556.1	Q61733.1	P82909.1	P21953.1
Q9CHK3.1	Q9BYD6.1	Q9BYC9.1	Q96A35.1	Q9P0J6.1	P04035.1	Q99714.1	B2RLH8.1
P62277.1	P08708.1	P62269.1	P63220.1	P62851.1	P62273.1	P62861.1	P46781.1

P08865.1	P17643.1	Q9H0D6.1	F5HCM1.1	E5RK45.1	A0A0B7JKK9.1	A1JIP3.1	B2RKS6.1
P0A6F5.1	P0C0Z7.1	Q49375.1	Q9Z708.1	P0A521.1	P42384.1	P0A520.1	P9WPE7.1
P10809.1	P10155.1	P05388.1	P05386.1	P05387.1	P27635.1	P62906.1	P40429.1
P35268.1	A8MUS3.1	P62750.1	P61353.1	P46776.1	P46779.1	P47914.1	P39023.1
P62888.1	Q02878.1	P18124.1	P62917.1	P32969.1	Q6SW59.1	P08253.1	P11021.1
Q969T7.1	Q76LX8.1	C6AV76.1	Q2FWL5.1	B1RDC1.1	Q2G2D8.1	P42684.1	Q8IZT6.1
Q9Y4K1.1	P02709.1	P02710.1	P02711.1	P04756.1	P02708.1	P02712.1	P11230.1
Q07001.1	P02715.1	Q04844.1	P07510.1	P13536.1	F1N690.1	M9YGB9.1	O43427.1
P68133.1	P62736.1	P60709.1	P63261.1	Q9NQW6.1	O15144.1	Q9H981.1	Q8N3C0.1
Q6VMQ6.1	Q6JQN1.1	Q5T8D3.1	P82987.1	Q6ZMM2.1	Q9NZK5.1	Q8IUX7.1	Q9NP61.1
Q9UJY4.1	O43488.1	P07897.1	P16112.1	Q73ZL3.1	Q92667.1	P49588.1	C9JKR2.1
F8ELD9.1	P15121.1	F5HF49.1	P05186.1	P55008.1	Q5STX8.1	P02763.1	P01009.1
P35368.1	P04217.1	P25100.1	P08697.1	P18825.1	P02765.1	P01023.1	P12814.1
O43707.1	P35611.1	Q9UBT7.1	P61163.1	P02489.1	P02511.1	P06733.1	P06280.1
Q16352.1	Q96Q83.1	P37840.1	Q9UJX4.1	P01019.1	Q9P2G1.1	Q9H8Y5.1	Q8N6D5.1
H0YKS4.1	P04083.1	P50995.1	P07355.1	P08758.1	P08133.1	Q9NQ90.1	Q03518.1
P01008.1	Q10567.1	Q9BXS5.1	Q96CW1.1	O00203.1	P02647.1	P02652.1	P06727.1
P04114.1	P02655.1	C9JX71.1	P05090.1	P02649.1	Q9BZR8.1	P03182.1	Q9BRQ8.1
Q9ATL6.1	P47863.1	P55087.1	P55064.1	P20292.1	Q15057.1	Q96P48.1	P35869.1
Q5VUY2.1	P03928.1	P25705.1	P06576.1	P56385.1	Q9DB20.1	P18859.1	Q9BZC7.1
Q8WWZ7.1	Q9NUT2.1	P61221.1	P53396.1	A1JNN2.1	P0A6G7.1	Q9H2U1.1	Q14562.1
O84848.1	P78508.1	Q99712.1	P17342.1	Q99856.1	Q8IVW6.1	Q96GD4.1	Q8WXX7.1
O15392.1	P02730.1	P98160.1	F8W034.1	P20749.1	P41182.1	Q9NYF8.1	Q6W2J9.1
Q8NFU0.1	P15291.1	P07550.1	P02749.1	P61769.1	Q13425.1	Q562R1.1	P42025.1
P13929.1	F0K2P6.1	O43252.1	Q13057.1	Q8IUF8.1	Q8NFC6.1	P18577.1	Q5VSJ8.1
Q02161.1	P02663.1	P02769.1	Q9NWK9.1	O95415.1	Q7Z569.1	Q99728.1	Q9P287.1
Q9NRL2.1	Q9UIF9.1	Q58F21.1	P25440.1	Q15059.1	O60885.1	P18892.1	Q8NCU7.1
P04003.1	O75844.1	P12830.1	P33151.1	Q8NE86.1	P62158.1	P07384.1	P17655.1
P20810.1	P27797.1	O94985.1	P10644.1	P31321.1	P13861.1	O70739.1	Q8QVL3.1
Q8QVL6.1	Q8QVL9.1	Q91CY5.1	Q91CZ6.1	Q98Y63.1	Q99AQ9.1	Q9DTD4.1	Q9DUB7.1
Q9DUC1.1	Q9JG76.1	Q9QU30.1	Q9QUB8.1	Q80AR5.1	Q80QT8.1	Q8UZK7.1	P14348.1
Q9H2A9.1	P00918.1	P16870.1	O75339.1	O15519.1	Q14790.1	P04040.1	P35221.1
P49913.1	P07858.1	P07339.1	P25774.1	Q03135.1	Q16663.1	Q9H9A5.1	Q9Y5K6.1
P09326.1	P14209.1	Q99741.1	O00311.1	O75794.1	P04637.1	B2RD01.1	Q03188.1
P49454.1	Q9HC77.1	Q02224.1	P00450.1	P08622.1	P35514.1	Q05980.1	P9WMJ9.1
Q9H444.1	P36222.1	O00299.1	P05108.1	O15335.1	Q6UVK1.1	Q9P2D1.1	P10645.1
O75390.1	O14503.1	Q00610.1	P09497.1	O75508.1	P56750.1	Q9P2I0.1	Q7Z460.1
O75122.1	O75153.1	P10909.1	Q7Z401.1	P00451.1	P00488.1	P48444.1	P61923.1
E9PP50.1	P23528.1	Q8WUD4.1	Q49A88.1	Q16204.1	P38432.1	P02452.1	P02458.1
P05539.1	P02462.1	G1K238.1	Q7SIB2.1	P20908.1	Q02388.1	P27658.1	P12107.1
Q99715.1	Q05707.1	P39059.1	Q9UMD9.1	P08123.1	P08572.1	Q7SIB3.1	P05997.1
P12110.1	P13942.1	F1MZU6.1	Q01955.1	P12111.1	P02745.1	P02746.1	P09871.1
P01024.1	P0C0L5.1	P01031.1	Q07021.1	P13671.1	P02748.1	P08603.1	Q03591.1
Q6PUV4.1	W1Q7Z5.1	Q15021.1	Q15003.1	P42695.1	Q14746.1	Q9NZB2.1	Q12860.1
Q02246.1	P78357.1	Q9UBW8.1	P36717.1	P02741.1	P12277.1	P06732.1	H0Y8U5.1
Q13618.1	Q86VP6.1	P25024.1	P16220.1	P06493.1	P11802.1	Q00534.1	P50750.1
P41002.1	P04080.1	P50238.1	P52943.1	O14957.1	P20674.1	P10606.1	P14854.1
P15954.1	P10176.1	Q16678.1	P10635.1	Q14008.1	Q9Y5Y2.1	Q96KP4.1	P14416.1
Q5QP82.1	P07585.1	E5RFJ0.1	Q86SQ9.1	Q9Y394.1	P49366.1	Q5QJE6.1	P24855.1
Q02413.1	P32926.1	P15924.1	Q16760.1	P19572.1	A9NHS5.1	Q9JZ09.1	P06959.1
P08461.1	P10515.1	P20285.1	P0AFG6.1	Q5F875.1	P19262.1	P36957.1	Q16555.1
P53634.1	Q14689.1	Q13443.1	Q12959.1	Q15398.1	Q16531.1	P40692.1	P43246.1
P09884.1	P03198.1	P04293.1	Q9NRF9.1	Q9UGP5.1	P89471.1	Q13426.1	P49736.1
P33992.1	P11387.1	Q02880.1	Q9UBZ4.1	P24928.1	O14802.1	Q9NW08.1	P31689.1
P25686.1	O60216.1	O95793.1	P55265.1	Q6P0N6.1	Q13202.1	Q8IVF4.1	E9PEB9.1
Q9UII4.1	P11161.1	Q14258.1	Q9ULT8.1	O95714.1	Q7Z6Z7.1	Q9Y4L5.1	O43567.1
Q63HN8.1	Q969K3.1	Q8IUQ4.1	P19474.1	Q6AZZ1.1	Q9C026.1	Q14669.1	Q5T4S7.1
P18146.1	Q05BV3.1	Q6ZMW3.1	O95967.1	P15502.1	Q9BY07.1	P13804.1	Q6PJG2.1
A6PW80.1	P68104.1	P13639.1	Q96RP9.1	Q9BW60.1	Q9UI08.1	P17813.1	Q9NZ08.1
P14625.1	Q14511.1	Q6P2E9.1	B2RLL7.1	O84591.1	Q9Z7A6.1	P03188.1	P04578.1

P14075.1	Q6SW67.1	Q92817.1	P12724.1	Q12929.1	P61916.1	P07099.1	P03211.1
P12978.1	P12977.1	P03203.1	P03204.1	Q99808.1	P27105.1	P03372.1	P32519.1
Q15723.1	P60842.1	Q14240.1	P38919.1	P41567.1	Q14152.1	B5ME19.1	P60228.1
O75821.1	Q13347.1	Q9Y262.1	F1TIN3.1	Q96KP1.1	Q96A65.1	O84646.1	Q01780.1
P30822.1	O14980.1	P41180.1	P15311.1	Q08945.1	P52907.1	Q9BXW9.1	Q14296.1
Q16658.1	Q7L8L6.1	Q7L5A8.1	P49327.1	Q8IX29.1	Q8TB52.1	Q7Z6M2.1	Q7L513.1
Q9BZ67.1	A1ZL39.1	P02792.1	P35555.1	P02671.1	P02675.1	P02679.1	Q06828.1
P02751.1	Q4ZHG4.1	P20930.1	P21333.1	P30043.1	O75955.1	Q14254.1	P49771.1
Q12841.1	Q13461.1	P32314.1	O95954.1	P04075.1	P09972.1	P07954.1	Q9H0Q3.1
Q7Z6J4.1	P30279.1	P30281.1	O96020.1	O95067.1	P14078.1	P51570.1	Q08380.1
O00214.1	Q3B8N2.1	P34903.1	P09104.1	A4D1B5.1	P17900.1	P06396.1	Q12789.1
Q8WUA4.1	P03300.1	P08292.1	P27958.1	P03995.1	P14136.1	P47871.1	Q8TDQ7.1
P35575.1	Q9NQR9.1	Q9Z186.1	P11413.1	P06744.1	P48318.1	Q99259.1	P48320.1
Q05329.1	Q05683.1	P00367.1	Q05586.1	Q5VSF9.1	Q12879.1	S0G235.1	P15104.1
Q06210.1	P35754.1	P18283.1	P09211.1	P04406.1	Q9NPB8.1	P11216.1	P06737.1
P11217.1	Q31BS5.1	P04921.1	O43292.1	P30419.1	D6RB28.1	Q96S52.1	Q969N2.1
Q86SQ4.1	Q9HC97.1	K7EQ05.1	P28799.1	P0A6P5.1	P44536.1	Q8WWP7.1	P62826.1
P16520.1	P09471.1	Q9BVP2.1	Q9NVN8.1	P00738.1	Q9Y6N9.1	Q96CS2.1	P48723.1
Q0VDF9.1	P08107.1	P34931.1	P11142.1	P04792.1	P07900.1	Q14568.1	P08238.1
P54652.1	Q15477.1	P03452.1	P69905.1	P68871.1	P02042.1	P69892.1	P02790.1
Q14CZ8.1	P09651.1	Q32P51.1	P14866.1	Q8WVV9.1	O43390.1	Q1KMD3.1	O88569.1
P22626.1	Q9Y241.1	O95263.1	P12314.1	P09429.1	P26583.1	P25021.1	P49773.1
Q9NQE9.1	P12081.1	Q9NVP2.1	Q8WUI4.1	Q9H0E3.1	P07305.1	Q02539.1	P16403.1
P16402.1	P10412.1	P16401.1	P0CE15.1	Q92522.1	P0C0S8.1	P0C0S9.1	Q93077.1
Q9BTM1.1	Q71UI9.1	P0C0S5.1	P16104.1	P62808.1	P33778.1	P62807.1	P10853.1
P06899.1	O60814.1	Q99877.1	Q16778.1	Q5QNW6.1	P57053.1	P68431.1	P68432.1
Q16695.1	Q71DI3.1	P49450.1	P62803.1	P62805.1	P62806.1	Q99525.1	P02259.1
Q9NR48.1	P01892.1	P04439.1	P16188.1	P10314.1	P01891.1	P10316.1	P13747.1
P30464.1	P03989.1	P30685.1	P18463.1	Q95365.1	P30480.1	P30484.1	P30486.1
P18464.1	P30490.1	P30495.1	P01889.1	Q31612.1	P30460.1	Q07000.1	Q29960.1
F8W9Z8.1	Q29963.1	P10321.1	P28068.1	P20036.1	P04440.1	P01909.1	P01906.1
E9PIB1.1	P01920.1	Q5Y7D6.1	P01903.1	P79483.1	P13762.1	Q30154.1	P04229.1
P20039.1	Q95IE3.1	Q5Y7A7.1	P01911.1	Q29974.1	P01912.1	P13760.1	Q9GZN2.1
Q9H2X6.1	Q9H422.1	P51610.1	P50502.1	295441875.1	295413967.1	295413927.1	295413946.1
295441907.1	295441886.1	295413949.1	312192955.1	295413970.1	295413952.1	295413922.1	295413835.1
295413838.1	295413935.1	295413976.1	P01880.1	Q9Y6R7.1	Q9Y5U9.1	Q5VY09.1	O14498.1
P78318.1	O00410.1	P11314.1	Q9BY32.1	P01317.1	A6XGL2.1	P01308.1	F8WCM5.1
P01325.1	P01326.1	O15503.1	Q13429.1	P01344.1	Q9Y287.1	O60478.1	Q8N201.1
P23229.1	Q13349.1	P08514.1	P05106.1	P16144.1	Q9H0C8.1	Q14624.1	Q9UMF0.1
P01562.1	P01563.1	P01574.1	P38484.1	P14316.1	Q15306.1	Q13568.1	P20591.1
P20592.1	Q9BYX4.1	O14879.1	Q12905.1	Q12906.1	P42701.1	Q5TF58.1	Q9NZM3.1
P03956.1	Q9Y547.1	Q13099.1	O60306.1	O84606.1	Q9Y283.1	P10997.1	Q05084.1
Q9P266.1	Q53G59.1	P13645.1	P02533.1	P08779.1	Q04695.1	P05783.1	P35527.1
P04264.1	P35908.1	P12035.1	P48668.1	P08729.1	Q07666.1	Q96EK5.1	P52732.1
Q96Q89.1	Q99661.1	P01042.1	Q6NY19.1	Q13601.1	Q04760.1	P42166.1	P19137.1
P11047.1	O43813.1	P0CC04.1	P23700.1	P46379.1	Q6SW84.1	P13285.1	O75845.1
P40126.1	Q99538.1	P29536.1	P02750.1	Q15345.1	Q8NHL6.1	Q8NHJ6.1	Q6GTX8.1
Q9NPC1.1	Q14847.1	P61968.1	P11182.1	P18428.1	P50851.1	P06858.1	P0A5J0.1
P9WK61.1	Q86W92.1	P05451.1	P23141.1	P07195.1	P31994.1	P31995.1	P01130.1
Q7Z4F1.1	A4QPB2.1	P20132.1	P05455.1	P18627.1	Q13094.1	P01374.1	Q8NHM5.1
O60341.1	P10253.1	O00754.1	P10619.1	Q13571.1	P11279.1	Q9UQV4.1	P22897.1
P14174.1	P34810.1	Q8NDA8.1	P06491.1	P07199.1	F5HDQ6.1	P03227.1	Q14764.1
P08392.1	P40925.1	P40926.1	Q8N5Y2.1	Q9ULC4.1	Q96IJ6.1	H3BT46.1	P11226.1
Q8WXG6.1	Q92585.1	P43243.1	P50281.1	P51512.1	Q9NPA2.1	P03485.1	Q96RN5.1
A6ZJ87.1	Q99705.1	P40967.1	Q01726.1	Q16655.1	P15529.1	190341000.1	F5HB52.1
O00562.1	P16035.1	P56192.1	Q9UBB5.1	Q29983.1	Q16891.1	P55082.1	P55083.1
P46821.1	P27816.1	Q9UPY8.1	Q9Y2H9.1	Q504T8.1	Q8N183.1	P03107.1	P26539.1

P36745.1	P50799.1	Q81023.1	Q8TCT9.1	Q9H2D1.1	O60830.1	O94826.1	Q8IWA4.1
P28482.1	Q16584.1	O43318.1	O43683.1	Q9Y3D0.1	P08571.1	E7EWX8.1	Q99549.1
Q04360.1	Q96T58.1	Q8WXI7.1	Q9H8L6.1	P11229.1	P20309.1	Q5VZF2.1	O00499.1
P01106.1	P02687.1	P25188.1	P25274.1	P81558.1	F7A0B0.1	P02686.1	P02689.1
P25189.1	P60201.1	P60202.1	P20916.1	Q13875.1	E9PG44.1	Q16653.1	Q5SUK5.1
P24158.1	P41218.1	Q969H8.1	Q8WXC6.1	P05164.1	Q9NPC7.1	Q9H1R3.1	P35749.1
P35579.1	Q09013.1	O95248.1	O14745.1	O84639.1	P15586.1	P54450.1	Q8IXJ6.1
O95167.1	O95298.1	P19404.1	O75251.1	Q6N069.1	Q73WP1.1	Q86VF7.1	Q9BT67.1
O75113.1	Q15843.1	Q13564.1	Q8IXH7.1	P58400.1	P58401.1	Q09666.1	P12036.1
P07196.1	P07197.1	Q8NEJ9.1	Q13491.1	P59665.1	P08246.1	Q9Y6K9.1	Q9NV10.1
P43490.1	Q14112.1	Q5JPE7.1	P69849.1	O95897.1	Q13253.1	P05114.1	P05204.1
P80272.1	Q15233.1	P29597.1	P23497.1	P08651.1	Q14938.1	Q16236.1	P19838.1
Q6P4R8.1	O75694.1	P52948.1	P11654.1	Q8TEM1.1	Q9QY81.1	B4DW92.1	Q9Y6Q9.1
Q9H1E3.1	P67809.1	Q9H8H0.1	P78316.1	O00567.1	Q9Y2X3.1	Q9NR30.1	P19338.1
O75607.1	Q8NFH5.1	P03466.1	P0C025.1	Q99733.1	Q12830.1	Q96RS6.1	Q9H209.1
A6NMS3.1	P23515.1	Q9HD40.1	295413917.1	295413964.1	295441897.1	Q9PWU2.1	P0C675.1
P11926.1	P54368.1	P10451.1	A2T3P5.1	A2T3T2.1	Q8TAD7.1	Q9BXB4.1	Q9UBL9.1
P03262.1	Q96ST3.1	P50897.1	Q8IXS6.1	Q6ZV29.1	Q6ZW49.1	Q9UBV8.1	Q15154.1
O60664.1	Q01453.1	O60437.1	P32119.1	O43808.1	Q13794.1	Q9H2J4.1	Q8IZ21.1
Q92903.1	O95674.1	Q9UKL6.1	P04180.1	P30086.1	O00329.1	P42356.1	O14986.1
P57054.1	O95394.1	E4NG02.1	P00558.1	P18669.1	P15259.1	Q96FE7.1	Q9Y263.1
Q13393.1	P26276.1	Q2FZ93.1	B2RID6.1	Q9Y617.1	P05155.1	P00747.1	O25249.1
P13796.1	P07359.1	P16234.1	Q96CS7.1	Q9H7P9.1	Q15149.1	O43660.1	Q8IUK5.1
Q6UX71.1	P09874.1	Q460N5.1	Q9UKK3.1	Q15365.1	Q15366.1	Q9BY77.1	A6Q6E9.1
B2RGP7.1	295413956.1	I6XH73.1	Q96FM1.1	O43525.1	P19156.1	P18434.1	P0CG38.1
Q16633.1	O84616.1	O75915.1	O84647.1	P68950.1	P02545.1	Q6P2Q9.1	O43143.1
Q9HCS7.1	Q96IZ0.1	P9WQ27.1	O84288.1	Q92841.1	Q15751.1	Q7Z333.1	O84419.1
O84818.1	B2RJ72.1	Q8N0Y7.1	O60312.1	Q9UHA3.1	P89479.1	Q9H3G5.1	Q02809.1
P07737.1	Q8WUM4.1	Q53EL6.1	P49683.1	P12004.1	Q9UQ80.1	Q7Z6L0.1	Q07954.1
P13674.1	C9JIZ6.1	Q9H7Z7.1	P40306.1	P49720.1	P28074.1	O60678.1	O14744.1
P03189.1	P78543.1	O75629.1	O84583.1	O60888.1	P30101.1	Q14554.1	Q96JJ7.1
P03129.1	Q9H8V3.1	Q96PZ2.1	Q8WU58.1	Q96IP4.1	Q92636.1	Q96JP0.1	Q4ZG55.1
Q9ULI3.1	Q96ST2.1	Q7Z3U7.1	P33215.1	Q8NHV4.1	Q9UFN0.1	O60502.1	Q6UWS5.1
Q86U86.1	P23297.1	P60903.1	P06702.1	P04271.1	Q9UPN6.1	Q6PI26.1	Q6ZMD2.1
Q9BVV6.1	P14079.1	Q8WUY1.1	P50616.1	O15027.1	Q15436.1	Q15437.1	D4ACF2.1
Q9QJ57.1	Q9QJ42.1	Q70J99.1	Q9GZT5.1	B1AQ67.1	Q9UM07.1	P21980.1	Q92954.1
Q96JQ0.1	Q9JZQ0.1	A6NMY6.1	Q6FDV9.1	Q5VTE0.1	548558395.1	Q2VIR3.1	Q58FF8.1
Q9HCE1.1	P13985.1	A2RGE9.1	Q8IXJ9.1	Q6P2P2.1	D3HT40.1	P42588.1	56160925.1
Q53H96.1	P08559.1	H0YD97.1	O00330.1	P14618.1	Q9BXR0.1	Q9H974.1	Q9H2M9.1
P35241.1	Q14699.1	P0DJD1.1	Q9BYM8.1	A6NK89.1	P61106.1	B2RHG7.1	P04626.1
Q13546.1	Q92932.1	Q16849.1	P78509.1	P03209.1	P35249.1	P15927.1	P27694.1
O75678.1	Q14257.1	Q9NQC3.1	Q9BZR6.1	P10276.1	P10826.1	P49788.1	Q8TC12.1
P10745.1	P02753.1	P52566.1	Q7Z6I6.1	Q9BRR9.1	Q15052.1	Q8IY67.1	P11908.1
Q15418.1	Q9UK32.1	O43159.1	Q9ULK6.1	Q7L0R7.1	Q9C0B0.1	Q9H0A0.1	O00472.1
P18333.1	Q6PD62.1	Q9NTZ6.1	Q5T481.1	Q96EV2.1	Q9BQ04.1	P35637.1	Q9UKM9.1
P22087.1	Q9Y230.1	P31153.1	Q9NSC2.1	O94885.1	Q93084.1	P08168.1	P10523.1
Q9BQB4.1	O14828.1	Q13018.1	Q9UHJ6.1	Q9H4L4.1	Q9GZR1.1	Q15019.1	Q14141.1
O15270.1	Q92743.1	O43464.1	P49842.1	Q9BZL6.1	O15075.1	Q96GX5.1	Q8TD19.1
Q13153.1	F5GWT4.1	P63151.1	A6PVN5.1	Q06190.1	P53041.1	Q8N8A2.1	Q13315.1
P49591.1	Q86SQ7.1	P02787.1	P36952.1	Q14140.1	B7WNR0.1	P02768.1	Q9BYB0.1
Q5T123.1	Q9BZZ2.1	P67812.1	Q9BY50.1	P61009.1	P37108.1	P42224.1	Q92783.1
Q96FS4.1	Q9UIB8.1	O75094.1	Q55732.1	O00193.1	Q7Z3B0.1	P62304.1	P62306.1
P62308.1	P62314.1	P62316.1	P62318.1	P63162.1	P14678.1	P53814.1	Q13573.1
Q63008.1	P05023.1	Q96K37.1	Q9NQZ2.1	Q96L92.1	Q14515.1	Q13813.1	Q01082.1
P63208.1	P21453.1	P23246.1	M5JGM9.1	Q9NY15.1	Q7KZF4.1	Q9NQZ5.1	P16949.1
P05093.1	P08686.1	P36956.1	Q12772.1	Q7Z7C7.1	Q96BY9.1	P38646.1	P08254.1
Q14683.1	O95347.1	Q8IY18.1	P07566.1	P51649.1	P14410.1	O00391.1	O75897.1

Q8NDZ2.1	P00441.1	O14512.1	Q8IWZ8.1	Q6UWL2.1	Q8TAQ2.1	O15056.1	P60880.1
Q9UQF0.1	O15400.1	Q9UNK0.1	B4DHN5.1	O00560.1	Q16635.1	Q9Y490.1	Q8N9U0.1
O95271.1	D3YTG3.1	Q7Z7G0.1	Q9ULW0.1	P13686.1	Q86VP1.1	Q96F92.1	Q4KMP7.1
Q9UL17.1	P01730.1	Q99832.1	F5H7V9.1	P24821.1	Q9UKZ4.1	Q5VYS8.1	Q92563.1
Q8N6V9.1	Q9Y6M0.1	P04958.1	P05452.1	Q8NBS9.1	Q86V81.1	Q86YJ6.1	Q5VV42.1
P40225.1	P07996.1	P35442.1	P04818.1	P63313.1	P62328.1	P01266.1	H7C1F5.1
P07202.1	P16473.1	P21463.1	Q07157.1	Q9NR96.1	J3KNT7.1	Q9Y2L5.1	P03206.1
P37837.1	P20062.1	P51532.1	Q14241.1	Q7KZ85.1	P05412.1	A0AVK6.1	Q14469.1
P31629.1	P17275.1	Q8NHW3.1	Q9ULX9.1	P35716.1	Q06945.1	P57073.1	Q02447.1
Q02446.1	O15164.1	Q9BWW7.1	Q04726.1	Q04727.1	P02786.1	Q9Y4A5.1	P01137.1
Q15582.1	P61586.1	P37802.1	P29401.1	P69222.1	Q92616.1	P51571.1	Q14956.1
Q96GE9.1	P57088.1	Q9BXS4.1	Q9C0B7.1	Q9Y5L0.1	P02766.1	Q13428.1	Q5T2D2.1
Q07283.1	P22102.1	A2RCL1.1	Q8NDV7.1	Q6P9F5.1	Q6ZTA4.1	P04295.1	O14773.1
Q97HE9.1	Q9Y3I0.1	P17752.1	Q8IWU9.1	Q0VAP8.1	P68363.1	Q9BQE3.1	P07437.1
Q9H4B7.1	Q13885.1	Q13509.1	P04350.1	P68371.1	Q9BUF5.1	Q14679.1	O75347.1
O14788.1	P48023.1	P43489.1	P25445.1	Q8N726.1	Q99816.1	Q15672.1	P14679.1
P07101.1	P23458.1	Q9Y2R2.1	P29350.1	P78324.1	P08621.1	P17133.1	Q62376.1
P09012.1	P09234.1	O75643.1	Q9UMX0.1	Q9UHD9.1	Q9Y4E8.1	Q9UPT9.1	Q8NFA0.1
Q86T82.1	Q86UV5.1	O15205.1	P62979.1	H0Y5H6.1	Q14157.1	O00762.1	Q96LR5.1
P62253.1	P22314.1	A0AVT1.1	Q15386.1	Q92575.1	I6ZLG2.1	O15294.1	Q9DUC0.1
Q6ZRI6.1	Q9NSG2.1	Q9BWL3.1	Q9NZ63.1	P0C727.1	Q9ZDE9.1	Q89882.1	P39999.1
Q12965.1	A2A306.1	A2RGM0.1	A6NG79.1	B8ZS71.1	B8ZUA4.1	E7EPZ9.1	F8W7G7.1
H0Y335.1	J3KP29.1	M7PC26.1	M7PDR8.1	M7Q4Y3.1	Q5T8M8.1	Q7TWS5.1	S5U6K1.1
S5UMF6.1	S5USV8.1	W5Z3U0.1	Q9BSU1.1	Q49AR2.1	P69996.1	P06132.1	Q709C8.1
O75436.1	Q9UBQ0.1	Q96AX1.1	P32241.1	Q3ASL6.1	Q00341.1	P08670.1	P03180.1
P02774.1	P04004.1	Q01668.1	O00555.1	P27884.1	O43497.1	P04275.1	Q9Y279.1
Q16864.1	O75348.1	Q2M389.1	O75083.1	Q9UNX4.1	C9J016.1	Q8IWA0.1	Q6UXN9.1
Q2TAY7.1	P13010.1	P12956.1	Q9Y2T7.1	A1JUA3.1	O95625.1	Q8NAP3.1	Q96K80.1
Q9Y6R6.1	Q01954.1	Q9P243.1	Q96KR1.1	Q8IWU4.1	P25311.1		

Predicting the immunological response of an individual to a polypeptide antigen

Specific polypeptide antigens induce immune responses in only a fraction of human subjects. Currently, there is no diagnostic test that can predict whether a polypeptide antigen would likely induce an immune response in an individual. In particular, there is a need for a test that can predict whether a person is an immune responder to a vaccine or immunotherapy composition.

According to the present disclosure, the polypeptide antigen-specific T cell response of an individual is defined by the presence within the polypeptide of one or more fragments that may be presented by multiple HLA class I or multiple HLA class II molecules of the individual.

In some cases the disclosure involves a method of predicting whether a subject will have an immune response to administration of a polypeptide, wherein an immune response is predicted if the polypeptide is immunogenic according to any method described herein. A cytotoxic T cell response is predicted if the polypeptide comprises at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject. A helper T

cell response is predicted if the polypeptide comprises at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject. No cytotoxic T cell response response is predicted if the polypeptide does not comprise any amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject. No helper T cell response is predicted if the polypeptide does not comprise any amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject.

In some cases the polypeptide is an active component of a pharmaceutical composition, and the method comprises predicting the development or production of anti-drug antibodies (ADA) to the polypeptide. The pharmaceutical composition may be a drug selected from those listed in Table 8. According to the present disclosure, ADA development will occur if, or to the extent that, an active component polypeptide is recognised by multiple HLA class II molecules of the subject, resulting in a helper T cell response to support an antibody response to the active component. The presence of such epitopes (PEPIs) may predict the development of ADA in the subject. The method may further comprise selecting or recommending for treatment of the human subject administration to the subject of a pharmaceutical composition that is predicted to induce low or no ADA, and optionally further administering the composition to the subject. In other cases the method predicts that the pharmaceutical composition will induce unacceptable ADA and the method further comprises selecting or recommending or treating the subject with a different treatment or therapy. The polypeptide may be a checkpoint inhibitor. The method may comprise predicting whether the subject will respond to treatment with the checkpoint inhibitor.

Table 8 – Example drugs associated with ADA-related adverse events

Drug	**ADA-related adverse event**
Abciximab	anaphylaxis
Adalimumab	anti-drug antibodies and treatment failure
Basiliximab	anaphylaxis
Cetuximab	IgE, anaphlyaxis
Epoetin	Antibody-mediated pure red cell aplasia
Erythropoietin	pure red cell aplasia

Etanercept	no apparent effect on safety
Factor-IX	anaphylaxis
Infliximab	anaphylaxis
OKT3	anaphylaxis
Pegloticase	anti-dug antibody, treatment failure
rIFN-beta	anaphylaxis
recombinant factor VIII	anaphylaxis
Thrombopoietin	thrombocitopenia
Ustekinumab	anti-ustekinumab antibodies, affected treatment efficacy

There is also currently no test that can predict the likelihood that a person will have a clinical response to, or derive clinical benefit from, a vaccine or immunotherapy composition. This is important because currently T cell responses measured in a cohort of individuals participating in vaccine or immunotherapy clinical trials poorly correlate with clinical responses. That is, the clinical responder subpopulation is substantially smaller than the immune responder subpopulation. Therefore, to enable the personalization of vaccines and immunotherapies it is important to predict not only the likelihood of an immune response in a specific subject, but also whether the immune response induced by the drug will be clinically effective (e.g. can kill cancer cells or pathogen infected cells or pathogens).

The presence in a vaccine or immunotherapy composition of at least two polypeptide fragments (epitopes) that can bind to at least three HLA class I of an individual (≥2 PEPI3+) is predictive for a clinical response. In other words, if ≥2 PEPI3+ can be identified within the active ingredient polypeptide(s) of a vaccine or immunotherapy composition, then an individual is a likely clinical responder. A “clinical response” or “clinical benefit” as used herein may be the prevention of or a delay in the onset of a disease or condition, the amelioration of one or more symptoms, the induction or prolonging of remission, or the delay of a relapse or recurrence or deterioration, or any other improvement or stabilisation in the disease status of a subject. Where appropriate, a “clinical response” may correlate to “disease control” or an “objective response” as defined by the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines.

In some cases the disclosure involves a method of predicting whether the subject will have a clinical response to administration of a pharmaceutical composition such as a vaccine or immunotherapy composition comprising one or more polypeptides as active ingredients. The method may comprise determining whether the one or more polypeptides together comprise at least two different sequences each of which is a T cell epitope capable of binding to at least two, or in some cases at least three HLA class I molecules of the subject; and predicting that the subject will have a clinical response to administration of the pharmaceutical composition if the one or more polypeptides together comprise at least two different sequences each of which is a T cell epitope capable of binding to at least two, or in some cases at least three HLA class I molecules of the subject; or that the subject will not have a clinical response to administration of the pharmaceutical composition if the one or more polypeptides together comprise no more that one sequence that is a T cell epitope capable of binding to at least two, or in some cases at least three HLA class I molecules of the subject.

For the purposes of this method two T cell epitopes are "different" from each other if they have different sequences, and in some cases also if they have the same sequence that is repeated in a target polypeptide antigen. In some cases the different T cell epitopes in a target polypeptide antigen do not overlap with one another.

In some cases all of the fragments of one or more polypeptides or active ingredient polypeptides that are immunogenic for a human subject are identified using the methods described herein. The identification of at least one fragment of the polypeptide(s) that is a T cell epitope capable of binding to at least two, or at least three HLA class I molecules of the subject predicts that the polypeptide(s) will elicit or is likely to elicit a cytotoxic T cell response in the subject. The identification of at least one fragment of the polypeptide(s) that is a T cell epitope capable of binding to at least two, or at least three, or at least four HLA class II molecules of the subject predicts that the polypeptide(s) will elicit or is likely to elicit a helper T cell response in the subject. The identification of no fragments of the polypeptide(s) that are T cell epitopes capable of binding to at least two, or at least three HLA class I molecules of the subject predicts that the polypeptide(s) will not elicit or is not likely to elicit a cytotoxic T cell response in the

subject. The identification of no fragments of the polypeptide(s) that are T cell epitopes capable of binding to at least two, or at least three, or at least four HLA class II molecules of the subject predicts that the polypeptide(s) will not elicit or is not likely to elicit a helper T cell response in the subject. The identification of at least two fragments of one or more active ingredient polypeptides of a vaccine or immunotherapy composition, wherein each fragment is a T cell epitope capable of binding to at least two, or at least three HLA class I molecules of the subject predicts that the subject is more likely to have, or will have a clinical response to the composition. The identification of less than two fragments of the one or more polypeptides that are T cell epitopes capable of binding to at least two, or at least three HLA class I molecules of the subject predicts that the subject is less likely to have, or will not have, a clinical response to the composition.

Without wishing to be bound by theory, one reason for the increased likelihood of deriving clinical benefit from a vaccine/immunotherapy comprising at least two multiple-HLA binding PEPIs, is that diseased cell populations, such as cancer or tumor cells or cells infected by viruses or pathogens such as HIV, are often heterogenous both within and between affected subjects. A specific cancer patient, for example, may or may not express or overexpress a particular cancer associated target polypeptide antigen of a vaccine, or their cancer may comprise heterogeneous cell populations, some of which (over-)express the antigen and some of which do not. In addition, the likelihood of developing resistance is decreased when more multiple HLA-binding PEPIs are included or targeted by a vaccine/immunotherapy because a patient is less likely to develop resistance to the composition through mutation of the target PEPI(s).

The likelihood that a subject will respond to treatment is therefore increased by (i) the presence of more multiple HLA-binding PEPIs in the active ingredient polypeptides; (ii) the presence of PEPIs in more target polypeptide antigens; and (iii) (over-)expression of the target polypeptide antigens in the subject or in diseased cells of the subject. In some cases expression of the target polypeptide antigens in the subject may be known, for example if target polypeptide antigens are in a sample obtained from the subject. In other cases, the probability that a specific subject, or diseased cells of a specific subject, (over-)express a specific or any combination of

target polypeptide antigens may be determined using population expression frequency data. The population expression frequency data may relate to a subject- and/or disease-matched population or the intent-to-treat population. For example, the frequency or probability of expression of a particular cancer-associated antigen in a particular cancer or subject having a particular cancer, for example breast cancer, can be determined by detecting the antigen in tumor, e.g. breast cancer tumor samples. In some cases such expression frequencies may be determined from published figures and scientific publications. In some cases a method of the invention comprises a step of determining the expression frequency of a relevant target polypeptide antigen in a relevant population.

Disclosed is a range of pharmacodynamic biomarkers to predict the activity/effect of vaccines in individual human subjects as well as in populations of human subjects. The biomarkers have been developed specifically for cancer vaccines, but similar biomarkers could be used for other vaccines or immunotherapy compositions. These biomarkers expedite more effective vaccine development and also decrease the development cost and may be used to assess and compare different compositions. Exemplary biomarkers are as follows.

- **AG95 – potency of a vaccine**: The number of antigens in a cancer vaccine that a specific tumor type expresses with 95% probability. AG95 is an indicator of the vaccine's potency, and is independent of the immunogenicity of the vaccine antigens. AG95 is calculated from the tumor antigen expression rate data. Such data may be obtained from experiments published in peer reviewed scientific journals. Technically, AG95 is determined from the binomial distribution of antigens in the vaccine, and takes into account all possible variations and expression rates.
- **PEPI3+ count – immunogenicity of a vaccine in a subject**: Vaccine-derived PEPI3+ are personal epitopes that bind to et least 3 HLAs of a subject and induce T cell responses. PEPI3+ can be determined using the PEPI3+ Test in subjects who's complete 4-digit HLA genotype is known.
- **AP count – antigenicity of a vaccine in a subject**: Number of vaccine antigens with PEPI3+. Vaccines contain sequences from target polypeptide antigens expressed by diseased cells. AP count is the number of antigens in the vaccine that contain PEPI3+, and the AP

count represents the number of antigens in the vaccine that can induce T cell responses in a subject. AP count characterizes the vaccine-antigen specific T cell responses of the subject since it depends only on the HLA genotype of the subject and is independent of the subject's disease, age, and medication. The correct value is between 0 (no PEPI presented by the antigen) and maximum number of antigens (all antigens present PEPIs).

- **AP50 – antigenicity of a vaccine in a population**: The mean number of vaccine antigens with a PEPI in a population. The AP50 is suitable for the characterization of vaccine-antigen specific T cell responses in a given population since it depends on the HLA genotype of subjects in a population.
- **AGP count – effectiveness of a vaccine in a subject**: Number of vaccine antigens expressed in the tumor with PEPI. The AGP count indicates the number of tumor antigens that vaccine recognizes and induces a T cell response against (hit the target). The AGP count depends on the vaccine-antigen expression rate in the subject's tumor and the HLA genotype of the subject. The correct value is between 0 (no PEPI presented by expressed antigen) and maximum number of antigens (all antigens are expressed and present a PEPI).
- **AGP50 – effectiveness of a cancer vaccine in a population**: The mean number of vaccine antigens expressed in the indicated tumor with PEPI (i.e., AGP) in a population. The AGP50 indicates the mean number of tumor antigens that the T cell responses induced by the vaccine can recognize. AGP50 is dependent on the expression rate of the antigens in the indicated tumor type and the immunogenicity of the antigens in the target population. AGP50 can estimate a vaccine's effectiveness in different populations and can be used to compare different vaccines in the same population. The computation of AGP50 is similar to that used for AG50, except the expression is weighted by the occurrence of the PEPI3+ in the subject on the expressed vaccine antigens. In a theoretical population, where each subject has a PEPI from each vaccine antigen, the AGP50 will be equal to AG50. In another theoretical population, where no subject has a PEPI from any vaccine antigen, the AGP50 will be 0. In general, the following statement is valid: $0 \leq AGP50 \leq AG50$.
- **mAGP – a candidate biomarker for the selection of likely responders:** Likelihood that a cancer vaccine induces T cell responses against multiple antigens expressed in the indicated tumor. mAGP is calculated from the expression rates of vaccine-antigens in e.g. the tumor

and the presence of vaccine derived PEPIs in the subject. Technically, based on the AGP distribution, the mAGP is the sum of probabilities of the multiple AGP (≥2 AGPs).

The results of a prediction as set out above may be used to inform a physician's decisions concerning treatment of the subject. Accordingly, in some cases the polypeptide is an active ingredient, for example of a vaccine or immunotherapy composition, the method of the disclosure predicts that the subject will have, is likely to have, or has above a threshold minimum likelihood of having an immune response and/or a clinical response to a treatmentcomprising administering the active ingredient polypeptide to the subject, and the method further comprises selecting the treatment for or selecting the vaccine or immunotherapy composition for treatment of the specific human subject. Also provided is a method of treatment with a subject-specific pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, wherein the pharmaceutical composition, kit or panel of polypeptides has been determined to have a threshold minimum likelihood of inducing a clinical response in the subject, wherein the likelihood of response has been determined using a method described herein. In some cases the minimum threshold is defined by one or more of the pharmacodynamic biomarkers described herein, for example a minimum PEPI3+ count (for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more PEPI3+), a minmum AGP count (for example AGP = at least 2 or at least 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more) and/or a minimum mAGP (for example AGP = at least 2 or at least 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more). For example, in some cases a subject is selected for treatment if their likelihood of a response targeted at a predefined number of target polypeptide antigens, optionally wherein the target polypeptide antigens are (predicted to be) expressed, is above a predetermined threshold (e.g. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more). Alternatively, the method may predict that the one or more polypeptide(s) of the composition will not elicit a T cell response and/or a clinical response in the subject and further comprise selecting a different treatment for the subject.

Predicting an autoimmune or toxic immune response to a polypeptide antigen

The differences among HLAs may influence the probability that a subject will experience immune-toxicity from a drug or polypeptide administered to the subject. There may be a toxic

immune response if a polypeptide administered to the subject comprises a fragment that corresponds to a fragment of an antigen expressed in normal healthy cells of the subject and that comprises an amino acid that is a T cell epitope capable of binding to multiple HLA class I molecules of the subject. Therefore, some cases in accordance with the disclosure, involve identifying a toxic immunogenic region or fragment of a polypeptide oridentifying subjects who are likely to experience immune-toxicity in response to administration of one or more polypeptides or a fragments thereof. The polypeptide may be an active ingredient of a vaccine or immunotherapy composition as described herein.

The method may comprise determining whether the polypeptide(s) comprises a sequence that is a T cell epitope capable of binding to at least two, or in other cases to at least three HLA class I molecules of the subject. In some cases the method comprises determining that the polypeptide comprises a sequence that is a T cell epitope capable of binding to at least four, or at least five HLA class I molecules of the subject; or an amino acid sequence that is a T cell epitope capable of binding to at least four, or at least five, or at least six or at least seven HLA class II of the subject. The method may further comprise identifying said sequence as toxic immunogenic for the subject or predicting a toxic immune response in the subject. In other cases no such amino acid sequence is identified and the method further comprises predicting no toxic immune response in the subject.The method may further comprise selecting or recommending for treatment of the subject administration of one or more polypeptides or a pharmaceutical composition that is predicted to induce no or low immune-toxicity, and optionally further treating the subject by administering the polypeptide. The disclosure also provides a method of treating a subject in need thereof by administrating to the subject such a polypeptide or composition.

In some cases a method described herein further comprises mutating a polypeptide that is predicted to be immunogenic for a subject, or that is predicted to be immunogenic in a proportion of subjects in a human population. Also provided is a method of reducing the immunogenicity of a polypeptide that has been identified as immunogenic in a subject or in a proportion of a human population as described herein. The polypeptide may be mutated to reduce the number of PEPIs in the polypeptide or to reduce the number of HLA class I or class II molecules of the subject or

of said population that bind to the fragment of the polypeptide that is identified as immunogenic in the subject or in a proportion of said population. In some cases the mutation may reduce or prevent a toxic immune response or may increase the efficacy by preventing the ADA development in the subject or in a proportion of said population. The mutated polypeptide may be further selected or recommended for treatment of the subject or of a subject of said population. The subject may further be treated by administration of the mutated polypeptide. The disclosure also provides a method of treating a subject in need thereof by administrating to the subject such a mutated polypeptide.

Predicting the immunological response of a human population to a polypeptide antigen

The methods described herein may be used to predict the response or response rate of a wider human population to administration of one or more polypeptides or compositions comprising one or more polypeptides. In some cases a method of the disclosure may be repeated for a plurality of human subjects to predict the response or response rate in those subjects. In other cases the method of the disclosure may be repeated for each subject in a relevant sample or model population of subjects and the results used to predict or define the response or response rate in a broader human population represented by the sample or model population. The sample/model population may be relevant to the intent-to-treat population for a pharmaceutical composition. A relevant population is one that is representative or similar to the population for whom or amongst whom treatment with the pharmaceutical composition is intended. In some cases the sample/model population is representative for the whole human race. In other cases the sample/model population may be disease- or subject-matched to the broader population (subpopulation), for example by ethnicity, geographical location, gender, age, disease or cancer, disease or cancer type or stage, genotype, expression of one or more biomarkers, partially by HLA genotype (for example subjects have one or more particular HLA alleles). For example, the sample/model population may have HLA class I and/or class II genomes that are representative of those found in the world population, or in subjects having a particular disease or condition, or ethnic background, from a particular geographical location, or having a particular disease-

associated biomarker (for example, women having the BRCA mutation for a breast cancer vaccine). In some cases the sample/model population is representative for at least 70%, or 75% or 80% or 84% or 85% or 86% or 90% or 95% of the broader population by HLA diversity and/or HLA frequency.

The method may comprise the step of selecting or defining a relevant sample or model population.. Each subject in the sample/model population is minimally defined by their HLA class I or class II genotype, e.g. complete 4-digit HLA class I genotype. Data concerning the HLA genotype of the sample/model population may be stored or recorded in or retrieved from a database or be an *in silico* model human population.

In some cases the methods described herein may be used to conduct an *in silico* clinical trial that predicts the proportion of immune-responders or the proportion of clinical responders in a population for a given drug, such as a vaccine or immunotherapy composition. This is useful for pre-selecting drugs that are likely to have high rates of efficacy to undergo clinical testing.

A population of individuals or a subpopulation of individuals can comprise the study cohort of an *in silico* clinical trial conducted with a drug. Each individual in the study cohort is characterized by its HLA genotype. The proportion of individuals in the study cohort having ≥1 PEPI2+, or ≥1 PEPI3+, or ≥1 PEPI4+, or ≥1 PEPI5+, derived from the polypeptides of the drug may be calculated. For the purposes of this disclosure we have termed this the "PEPI Score". Unless otherwise indicted, the "PEPI Score" refers specifically to the ≥1 PEPI3+ Score. This PEPI Score predicts the proportion of subjects with T cell responses in a clinical trial conducted with the same drug in a relevant cohort of subjects.

The disclosure provides a method of conducting an *in silico* trial for a vaccine or immunotherapy composition having one or more polypeptide active ingredients. The *in silico* trial may predict the cytotoxic T cell response rate of a human population. The method may comprise:(i) selecting or defining an *in silico* model human population comprising a plurality of subjects each defined by HLA class I genotype, wherein the *in silico* model human population may correspond to or be representative of, or relevant to the intend-to-treat, said human population in which the cytotoxic T cell response rate is to be predicted; (ii) determining for each

subject in the *in silico* model human population whether the one or more active ingredient polypeptides comprise at least one sequence that is PEPI2+, PEPI3+, PEPI4+ or PEPI5+ (depending the the size, administration route and adjuvants of the polypeptide composition); and (iii) predicting the cytotoxic T cell response rate (of said human population), wherein a higher proportion of the *in silico* model human population that meet the requirements of step (ii) predicts a higher cytotoxic T cell response rate. The proportion of the *in silico* model human population that meet the requirements of step (ii) may correlate with or correspond to the predicted response rate in the intend-to-treat population.

Correlation between the presence of HLA-restricted epitopes and immune response rates and/or clinical response rates has not been demonstrated by clinical trials of the prior art. This raises the question about the mechanism of action of immunotherapies. The Examples provided herein show that activation of cytotoxic T lymphocytes (CTLs) against multiple targets may be required for a clinically meaningful response, for example against heterogeneous tumors. So far, CTL responses reported in clinical trials neither account for multiple targets nor for multiple HLAs. For example, a melanoma peptide vaccine targeting two antigens (Tyrosinase and gp100) elicited CTL responses in 52% of patients, but only 12% had clinical benefit . Using an *in silico* Model Population of 433 subjects we determined a ≥1 PEPI3+ Score of 42% (in 42% at least one vaccine-derived epitope could be identified that could be presented by at least three HLA class I of the subject) and a ≥2 PEPI3+ Score of 6% (in 6% at least two vaccine-derived epitopes could be identified that could be presented by at least three HLA class II of the subject). This explains why the clinical investigators did not find correlation between CTL response rate and clinical response rate in their trial: the peptides in the vaccine performed poorly in the trial because there were only a few patients in which two different vaccine peptides could both activate CTL responses. The discrepancy between the results of the clinical trial and our *in silico* trial is based on the different populations, since the populations of each had subjects with different HLA genotypes. However, the response rate results provided by the *in silico* trial on the Model Population are a good prediction for the response rate outcome in the clinical trial population.

Therefore disclosed herein is a method of conducting an *in silico* trial for a vaccine or immunotherapy composition having one or more active ingredient polypeptides. The *in silico* trial may predict the clinical response rate of a human population. The method may comprise (i) selecting or defining an *in silco* model human population comprising a plurality of subjects defined by HLA class I genotype, wherein the *in silico* model human population may correspond to or be representative of said human population (relevant to the intend-to-treatpopulation) in which the clinical response rate is to be predicted; (ii) determining for each subject in the *in silico* model human population whether the one or more active ingredient polypeptides comprise at least two different sequences each of which is a T cell epitope capable of binding to at least three, or at least four, or at least five HLA class I of the subject; and (iii) predicting the clinical response rate (of said human population), wherein a higher proportion of the *in silico* model human population that meet the requirements of step (ii) predicts a higher clinical response rate. The proportion of the *in silico* model human population that meet the requirements of step (ii) may correlate with or correspond to the predicted response rate in the intend-to-treat population.

An equivalent method may be used to predict, for example, the immune toxicity rate, checkpoint inhibitor response rate, ADA development rate, or helper T cell response rate of a human population (or subpopulation) to administration of a polypeptide or pharmaceutical composition comprising one or more polypeptides as active ingredients.

In some cases the method may be repeated for one or more further polypeptides or fragments thereof or vaccine or pharmaceutical or immunotherapy compositions. The polypeptides, fragments or compositions may be ranked according to their predicted response rates in said human population. This method is useful for selecting the most effective or most safe polypeptide drugs for the intent-to-treat population.

Design and preparation of pharmaceutical compositions

In some aspects the disclosure provides a method of designing or preparing a polypeptide, or a polynucleic acid that encodes a polypeptide, for inducing an immune response, a cytotoxic T

cell response or a helper T cell response in a human subject (e.g. in a target or intent-to-treat population). The disclosure also provides an immunogenic composition, or pharmaceutical composition, kit or panel of peptides, methods of designing or preparing the same, compositions that may be obtained by those methods, and their use in a method of inducing an immune response, a cytotoxic T cell response, or a helper T cell response in the subject, or a method of treating, vaccinating or providing immunotherapy to a subject.

The methods involve identifying and/or selecting a T cell epitope that binds to multiple, e.g. at least three HLA class I molecules of individual subjects across the target population with a high frequency, and designing or/or preparing a polypeptide that comprises one or more such epitopes (PEPI3+s). Such high frequency population PEPI3+s may be referred to herein as "bestEPIs". According to the present disclosure bestEPIs induce immune responses in a high proportion of human subjects in the specific or target human population. The polypeptide may be an active ingredient in a pharmaceutical composition or kit or panel of polypeptides for use in a method of treatment of a subject of the specific or target human population.

The composition/kit may optionally further comprise at least one pharmaceutically acceptable diluent, carrier, or preservative and/or additional polypeptides that do not comprise any bestEPIs. The polypeptides may be engineered or non-naturally occurring. The kit may comprise one or more separate containers each containing one or more of the active ingredient peptides. The composition/kit may be a personalised medicine to prevent, diagnose, alleviate, treat, or cure a disease of an individual, such as a cancer.

In some cases the bestEPI is capable of binding to multiple, for example to at least three HLA class I and/or to at least three HLA class II molecules of a high percentage of the subjects in a sample or model population, such as described herein. In some cases a "high" percentage may be at least or more than 1%, 2%, 5%, 10%, 12%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49% or 50% of the relevant population or subpopulation of human subjects. In some cases a "high" percentage is relative to the percentage of subjects in the population having other PEPI3+s. For example, the PEPI3+ may be

the most frequent in the population, or more frequent than 50%, or 55% or 60% or 65% or 70% or 75% or 80% or 85% or 90% or 95% or 97% or 99% of all PEPI3+ and/or PEPI4+ and/or PEPI4+ in one or more reference target polypeptide antigens.

In some cases the probability that the target polypeptide antigen is expressed in a subject of the specific or target population is taken into account to determine the overall likelihood that the bestEPI will induce an immune response that targets a polypeptide antigen that is expressed by a subject of the specific or target human population. In some cases the bestEPI is predicted to express both the relevant target polypeptide antigen and multiple, for example at least three HLA class I or at least three HLA class II molecules capable of binding to the bestEPI in at least or more than 1%, 2%, 5%, 10%, 12%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49% or 50% of the relevant population of human subjects.

In some cases multiple T cell epitopes/PEPI3+s, optionally from one or more target polypeptide antigens may be ranked by the percentage of subjects in the model or intend-to-treat population having multiple, for example at least three HLA class I or at least three HLA class II molecules capable of binding to each fragment; or by the percentage of subjects in the model or intend-to-treat population that are predicted to express both the target polypeptide antigen comprising the fragment and multiple, for example at least three HLA class I or at least three HLA class II molecules capable of binding to the fragments. The peptide or composition may be designed to comprise one or more PEPI3+s that are selected based on their ranking.

Typically each bestEPI is a fragment of a target polypeptide antigen and polypeptides that comprise one or more of the bestEPIs are the target polypeptide antigens for the treatment, vaccination or immunotherapy. The method may comprise the step of identifying one or more suitable target polypeptide antigens. Typically each target polypeptide antigen will be associated with the same disease or condition, pathogenic organism or group of pathogenic organisms or virus, or type of cancer.

The composition, kit or panel may comprise, or the method may comprise selecting, for each bestEPI a sequence of up to 50, 45, 40, 35, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10 or 9 consecutive amino acids of the target polypeptide antigen, such as a polypeptide described herein, which consecutive amino acids comprise the amino acid sequence of the bestEPI.

In some cases the amino acid sequence is flanked at the N and/or C terminus by additional amino acids that are not part of the consecutive sequence of the target polypeptide antigen. In some cases the sequence is flanked by up to 41 or 35 or 30 or 25 or 20 or 15 or 10, or 9 or 8 or 7 or 6 or 5 or 4 or 3 or 2 or 1 additional amino acid at the N and/or C terminus or between target polypeptide fragments. In other cases each polypeptide either consists of a fragment of a target polypeptide antigen, or consists of two or more such fragments arranged end to end (arranged sequentially in the peptide end to end) or overlapping in a single peptide (where two or more of the fragments comprise partially overlapping sequences, for example where two bestEPIs in the same polypeptide are within 50 amino acids of each other).

When fragments of different polypeptides or from different regions of the same polypeptide are joined together in an engineered peptide there is the potential for neoepitopes to be generated around the join or junction. Such neoepitopes encompass at least one amino acid from each fragment on either side of the join or junction, and may be referred to herein as junctional amino acid sequences. The neoepitopes may induce undesired T cell responses against healthy cells (autoimmunity). The peptides may be designed, or the polypeptides may be screened, to avoid, eliminate or minimise neoepitopes that correspond to a fragment of a protein expressed in normal healthy human cells and/or neoepitopes that are capable of binding to at least two, or in some cases at least three, or at least four HLA class I molecules of the subject, or in some cases at least two, or at least three or four or five HLA class II molceules of the subject. In some cases the peptide is designed, or the polypeptide screened, to eliminate polypeptides having a junctional neoepitope that is capable of binding in more than a threshold percentage of human subjects in a specific, target or model population, to at least two HLA class I molecules expressed by individual subjects of the population. In some cases the threshold is 30%, or 20%, or 15%, or 10%, or 5%, or 2%, or 1%, or 0.5% of said population. The methods of the disclosure may be

used to identify or screen for such neoepitopes as described herein. Alignment may be determined using known methods such as BLAST algorithms. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/).

The at least two bestEPIs of the composition polypeptides may both target a single antigen (e.g a polypeptide vaccine comprising two multiple HLA-binding PEPIs derived from a single antigen, for example a tumor associated antigen, targeted by the vaccine/immunotherapy) or may target different antigens (e.g. a polypeptide vaccine comprising one multiple HLA-binding PEPI derived from one antigen, e.g. a tumor associated antigen, and a second multiple HLA-binding PEPI derived from a different antigen, e.g. a different tumor associated antigen, both targeted by the vaccine/immunotherapy).

In some cases the active ingredient polypeptide(s) together comprise, or the method comprises selecting, a total of or at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 or more different bestEPIs. The bestEPIs may be fragments of one or more different target polypeptide antigens. By identifying the specific fragments of each target polypeptide antigen that are immunogenic for a high proportion of subjects in a target population it is possible to incorporate multiple such fragments, optionally from multiple different target polypeptide antigens, in a single active ingredient polypeptide or multiple active ingredient polypeptides intended for use in combination or to maximise the number of T cell clones that can be activated by one or more polypeptides of a certain length.

Currently most vaccines and immunotherapy compositions target only a single polypeptide antigen. However according to the present disclosure it is in some cases beneficial to provide a pharmaceutical composition or an active ingredient polypeptide that targets two or more different polypeptide antigens. For example, most cancers or tumors are heterogeneous, meaning that different cancer or tumor cells of a subject (over-)express different antigens. The tumour cells of different cancer patients also express different combinations of tumour-associated antigens. The anti-cancer immunogenic compositions that are most likely to be effective are

those that target multiple antigens expressed by the tumor, and therefore more cancer or tumor cells, in an individual human subject or in a population.

The beneficial effect of combining multiple bestEPIs in a single treatment (administration of one or more pharmaceutical compositions that together comprise multiple PEPIs), can be illustrated by the personalised vaccine polypeptides described in Examples 15 and 16 below. Exemplary CTA expression probabilities in ovarian cancer are as follows: BAGE: 30%; MAGE A9: 37%; MAGE A4: 34%; MAGE A10: 52%. If patient XYZ were treated with a vaccine comprising PEPIs in only BAGE and MAGE A9, then the probability of having a mAGP (multiple expressed antigens with PEPI) would be 11%. If patent XYZ were treated with a vaccine comprising only PEPIs for the MAGE A4 and MAGE A10 CTAs, then the probability of having a multiAGP would be 19%. However if a vaccine contained all 4 of these CTAs (BAGE, MAGE A9, MAGE A4 and MAGE A10), then the probability of having a mAGP would be 50%. In other words the effect would be greater than the combined probabilities of mAGP for both two-PEPI treatments (probability mAGP for BAGE/MAGE + probability mAGP for MAGE A4 and MAGE A10). Patient XYZ's PIT vaccine described in Example 15 contains a further 9 PEPIs, and thus, the probability of having a mAGP is over 99.95%.

Likewise exemplary CTA expression probabilities in breast cancer are as follows: MAGE C2: 21%; MAGE A1: 37%; SPC1: 38%; MAGE A9: 44%. Treatment of patient ABC with a vaccine comprising PEPIs in only MAGE C2: 21% and MAGE A1 has a mAGP probability of 7%. Treatment of patient ABC with a vaccine comprising PEPIs in only SPC1: 38%; MAGE A9 has a mAGP probability of 11%. Treatment of patient ABC with a vaccine comprising PEPIs in MAGE C2: 21%; MAGE A1: 37%; SPC1: 38%; MAGE A9 has a mAGP probability of 44% (44 > 7 + 11). Patient ABC's PIT vaccine described in Example 16 contains a further 8 PEPIs, and thus, the probability of having a mAGP is over 99.93%.

Accordingly in some cases the bestEPIs of the active ingredient polypeptides are from two or more different target polypeptide antigens, for example different antigens associated with a specific disease or condition, for example different cancer- or tumor-associated antigens or antigens expressed by a target pathogen. In some cases the PEPIs are from a total of or at least 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 or more different target polypeptide antigens. The different target polypeptide antigens may be any different polypeptides that it is useful to target or that can be selectively targeted with different PEPI3+s. In some cases different target polypeptide antigens are non-homologues or non-paralogues or have less than 95%, or 90%, or 85% or 80% or 75% or 70% or 60% or 50% sequence identity across the full length of each polypeptide. In some cases different polypeptides are those that do not share any PEPI3+s. Alternatively, in some cases the PEPI3+s are from different target polypeptide antigens when they are not shared with other polypeptide antigens targeted by the active ingredient polypeptides.

In some cases one or more or each of the immunogenic polypeptide fragments is from a polypeptide that is present in a sample taken from a human subject (e.g., of the target population). This indicates that the polypeptide is expressed in the subject, for example a cancer- or tumor-associated antigen or a cancer testis antigen expressed by cancer cells of the subject. In some cases one or more or each of the polypeptides is a mutational neoantigen, or an expressional neoantigen of the subject. One or more or each fragment may comprise a neoantigen specific mutation.

In other cases one or more or each of the immunogenic polypeptide fragments is from a target polypeptide antigen that is not generally expressed or is minimally expressed in normal healthy cells or tissue, but is expressed in a high proportion of (with a high frequency in) subjects or in the diseased cells of a subject having a particular disease or condition, as described above. The method my comprise identifying or selecting such a target polypeptide antigen. In some cases two or more or each of the immunogenic polypeptide fragments/bestEPIs are from different cancer- or tumor-associated antigens that are each (over-)expressed with a high frequency in subjects having a type of cancer or a cancer derived from a particular cell type or tissue. In some cases the immunogenic polypeptide fragments are from a total of or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 or 40 different cancer- or tumor-associated polypeptides. In some cases one or

more or each or at least one, at least two, at least three, at least four, at least five or at least six or at least seven of the polypeptides are selected from the antigens listed in any one of Tables 2 to 7.

In some cases one or more or each of the target polypeptide antigens is a cancer testis antigen (CTA). In some cases the immunogenic polypeptide fragments/bestEPIs are from at least 1, or at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 CTAs, or from a total of 3 or more different target polypeptide antigens, optionally wherein 1, 2, or all three or at least three are CTAs, or from 4 or more different polypeptide antigens, optionally wherein 1, 2, 3 or all four or at least 1, 2, 3 or 4 are CTAs, or from 5 or more different polypeptide antigens, optionally wherein 1, 2, 3, 4 or all five or at least 1, 2, 3, 4, or 5 are CTAs, or from 6 or more different polypeptide antigens, optionally wherein 1, 2, 3, 4, 5 or all six or at least 1, 2, 3, 4, 5, or 6 are CTAs, or from 7 or more different polypeptide antigens, optionally wherein 1, 2, 3, 4, 5, 6 or all 7 or at least 1, 2, 3, 4, 5, 6 or 7 are CTAs, or from 8 or more different polypeptide antigens, optionally wherein 1, 2, 3, 4, 5, 6, 7 or all 8 or at least 1, 2, 3, 4, 5, 6, 7 or 8 are CTAs. In some cases one or more or each of the target polypeptide antigens is expressed by a bacteria, a virus, or a parasite.

In some cases one or more of the polypeptide fragments comprises an amino acid sequence that is a T cell epitope capable of binding to at least two, or at least three HLA class I of of a high percentage of subjects in the populationsubject and one or more of the polypeptide fragments comprises an amino acid sequence that is a T cell epitope capable of binding to at least two, or at least three, or at least four HLA class II of the subject of a high percentage of subjects in the population, wherein the HLA class I and HLA class II binding fragments may optionally overlap. A composition prepared by such a method may elicit both a cytotoxic T cell response and a helper T cell response in the subject.

Immunogenic and Pharmaceutical Compositions, Methods of Treatment and Modes of Administration

In some aspects the disclosure relates to a pharmaceutical composition, kit, or panels of polypeptides as described above having one or more polypeptides as active ingredient(s). These

may be for use in a method of inducing an immune response, treating, vaccinating or providing immunotherapy to a subject, and the pharmaceutical composition may be a vaccine or immunotherapy composition. Such a treatment comprises administering one or more polypeptides or pharmaceutical compositions that together comprise all of the active ingredient polypeptides of the treatment to the subject. Multiple polypeptides or pharmaceutical compositions may be administered together or sequentially, for example all of the pharmaceutical compositions or polypeptides may be administered to the subject within a period of 1 year, or 6 months, or 3 months, or 60 or 50 or 40 or 30 days.

The immunogenic or pharmaceutical compositions or kits described herein may comprise, in addition to one or more immunogenic peptides, a pharmaceutically acceptable excipient, carrier, diluent, buffer, stabiliser, preservative, adjuvant or other materials well known to those skilled in the art. Such materials are preferably non-toxic and preferably do not interfere with the pharmaceutical activity of the active ingredient(s). The pharmaceutical carrier or diluent may be, for example, water containing solutions. The precise nature of the carrier or other material may depend on the route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intradermal, and intraperitoneal routes.

The pharmaceutical compositions of the disclosure may comprise one or more "pharmaceutically acceptable carriers". These are typically large, slowly metabolized macromolecules such as proteins, saccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, sucrose (Paoletti et al., 2001, Vaccine, 19:2118), trehalose (WO 00/56365), lactose and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to those of ordinary skill in the art. The pharmaceutical compositions may also contain diluents, such as water, saline, glycerol, etc. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present. Sterile pyrogen-free, phosphate buffered physiologic saline is a typical carrier (Gennaro, 2000, Remington: The Science and Practice of Pharmacy, 20th edition, ISBN:0683306472).

The pharmaceutical compositions of the disclosure may be lyophilized or in aqueous form, i.e. solutions or suspensions. Liquid formulations of this type allow the compositions to be

administered direct from their packaged form, without the need for reconstitution in an aqueous medium, and are thus ideal for injection. The pharmaceutical compositions may be presented in vials, or they may be presented in ready filled syringes. The syringes may be supplied with or without needles. A syringe will include a single dose, whereas a vial may include a single dose or multiple doses.

Liquid formulations of the disclosure are also suitable for reconstituting other medicaments from a lyophilized form. Where a pharmaceutical composition is to be used for such extemporaneous reconstitution, the disclosure provides a kit, which may comprise two vials, or may comprise one ready-filled syringe and one vial, with the contents of the syringe being used to reconstitute the contents of the vial prior to injection.

The pharmaceutical compositions of the disclosure may include an antimicrobial, particularly when packaged in a multiple dose format. Antimicrobials may be used, such as 2-phenoxyethanol or parabens (methyl, ethyl, propyl parabens). Any preservative is preferably present at low levels. Preservative may be added exogenously and/or may be a component of the bulk antigens which are mixed to form the composition (e.g. present as a preservative in pertussis antigens).

The pharmaceutical compositions of the disclosure may comprise detergent e.g. Tween (polysorbate), DMSO (dimethyl sulfoxide), DMF (dimethylformamide). Detergents are generally present at low levels, e.g. <0.01%, but may also be used at higher levels, e.g. 0.01 – 50%.

The pharmaceutical compositions of the disclosure may include sodium salts (e.g. sodium chloride) and free phosphate ions in solution (e.g. by the use of a phosphate buffer).

In certain embodiments, the pharmaceutical composition may be encapsulated in a suitable vehicle either to deliver the peptides into antigen presenting cells or to increase the stability. As will be appreciated by a skilled artisan, a variety of vehicles are suitable for delivering a pharmaceutical composition of the disclosure. Non-limiting examples of suitable structured fluid delivery systems may include nanoparticles, liposomes, microemulsions, micelles, dendrimers and other phospholipid-containing systems. Methods of incorporating pharmaceutical compositions into delivery vehicles are known in the art.

In order to increase the immunogenicity of the composition, the pharmacological compositions may comprise one or more adjuvants and/or cytokines.

Suitable adjuvants include an aluminum salt such as aluminum hydroxide or aluminum phosphate, but may also be a salt of calcium, iron or zinc, or may be an insoluble suspension of acylated tyrosine, or acylated sugars, or may be cationically or anionically derivatised saccharides, polyphosphazenes, biodegradable microspheres, monophosphoryl lipid A (MPL), lipid A derivatives (e.g. of reduced toxicity), 3-O-deacylated MPL [3D-MPL], quil A, Saponin, QS21, Freund's Incomplete Adjuvant (Difco Laboratories, Detroit, Mich.), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.), AS-2 (Smith-Kline Beecham, Philadelphia, Pa.), CpG oligonucleotides, bioadhesives and mucoadhesives, microparticles, liposomes, polyoxyethylene ether formulations, polyoxyethylene ester formulations, muramyl peptides or imidazoquinolone compounds (e.g. imiquamod and its homologues). Human immunomodulators suitable for use as adjuvants in the disclosure include cytokines such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc), macrophage colony stimulating factor (M-CSF), tumour necrosis factor (TNF), granulocyte, macrophage colony stimulating factor (GM-CSF) may also be used as adjuvants.

In some embodiments, the compositions comprise an adjuvant selected from the group consisting of Montanide ISA-51 (Seppic, Inc., Fairfield, N.J., United States of America), QS-21 (Aquila Biopharmaceuticals, Inc., Lexington, Mass., United States of America), GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete and incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT).

By way of example, the cytokine may be selected from the group consisting of a transforming growth factor (TGF) such as but not limited to TGF-α and TGF-β; insulin-like growth factor-I and/or insulin-like growth factor-II; erythropoietin (EPO); an osteoinductive factor; an interferon such as but not limited to interferon-.α, -β, and -γ; a colony stimulating factor (CSF) such as but not limited to macrophage-CSF (M-CSF); granulocyte-macrophage-CSF

(GM-CSF); and granulocyte-CSF (G-CSF). In some embodiments, the cytokine is selected from the group consisting of nerve growth factors such as NGF-β; platelet-growth factor; a transforming growth factor (TGF) such as but not limited to TGF-α. and TGF-β; insulin-like growth factor-I and insulin-like growth factor-II; erythropoietin (EPO); an osteoinductive factor; an interferon (IFN) such as but not limited to IFN-α, IFN-β, and IFN-γ; a colony stimulating factor (CSF) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); an interleukin (Il) such as but not limited to IL-1, IL-1.alpha., IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-13, IL-14, IL-15, IL-16, IL-17, IL-18; LIF; kit-ligand or FLT-3; angiostatin; thrombospondin; endostatin; a tumor necrosis factor (TNF); and LT.

It is expected that an adjuvant or cytokine can be added in an amount of about 0.01 mg to about 10 mg per dose, preferably in an amount of about 0.2 mg to about 5 mg per dose. Alternatively, the adjuvant or cytokine may be at a concentration of about 0.01 to 50%, preferably at a concentration of about 2% to 30%.

In certain aspects, the pharmaceutical compositions of the disclosure are prepared by physically mixing the adjuvant and/or cytokine with the PEPIs under appropriate sterile conditions in accordance with known techniques to produce the final product.

Examples of suitable compositions of polypeptide fragments and methods of administration are provided in Esseku and Adeyeye (2011) and Van den Mooter G. (2006). Vaccine and immunotherapy composition preparation is generally described in Vaccine Design ("The subunit and adjuvant approach" (eds Powell M. F. & Newman M. J. (1995) Plenum Press New York). Encapsulation within liposomes, which is also envisaged, is described by Fullerton, US Patent 4,235,877.

In some embodiments, the compositions disclosed herein are prepared as a nucleic acid vaccine. In some embodiments, the nucleic acid vaccine is a DNA vaccine. In some embodiments, DNA vaccines, or gene vaccines, comprise a plasmid with a promoter and appropriate transcription and translation control elements and a nucleic acid sequence encoding one or more polypeptides of the disclosure. In some embodiments, the plasmids also include

sequences to enhance, for example, expression levels, intracellular targeting, or proteasomal processing. In some embodiments, DNA vaccines comprise a viral vector containing a nucleic acid sequence encoding one or more polypeptides of the disclosure. In additional aspects, the compositions disclosed herein comprise one or more nucleic acids encoding peptides determined to have immunoreactivity with a biological sample. For example, in some embodiments, the compositions comprise one or more nucleotide sequences encoding 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more peptides comprising a fragment that is a T cell epitope capable of binding to at least three HLA class I molecules and/or at least three HLA class II molecules of a patient. In some embodiments, the peptides are derived from an antigen that is expressed in cancer. In some embodiments the DNA or gene vaccine also encodes immunomodulatory molecules to manipulate the resulting immune responses, such as enhancing the potency of the vaccine, stimulating the immune system or reducing immunosuppression. Strategies for enhancing the immunogenicity of of DNA or gene vaccines include encoding of xenogeneic versions of antigens, fusion of antigens to molecules that activate T cells or trigger associative recognition, priming with DNA vectors followed by boosting with viral vector, and utilization of immunomodulatory molecules. In some embodiments, the DNA vaccine is introduced by a needle, a gene gun, an aerosol injector, with patches, via microneedles, by abrasion, among other forms. In some forms the DNA vaccine is incorporated into liposomes or other forms of nanobodies. In some embodiments, the DNA vaccine includes a delivery system selected from the group consisting of a transfection agent; protamine; a protamine liposome; a polysaccharide particle; a cationic nanoemulsion; a cationic polymer; a cationic polymer liposome; a cationic nanoparticle; a cationic lipid and cholesterol nanoparticle; a cationic lipid, cholesterol, and PEG nanoparticle; a dendrimer nanoparticle. In some embodiments, the DNA vaccines is administered by inhalation or ingestion. In some embodiments, the DNA vaccine is introduced into the blood, the thymus, the pancreas, the skin, the muscle, a tumor, or other sites.

In some embodiments, the compositions disclosed herein are prepared as an RNA vaccine. In some embodiments, the RNA is non-replicating mRNA or virally derived, self-amplifying RNA. In some embodiments, the non-replicating mRNA encodes the peptides

disclosed herein and contains 5' and 3' untranslated regions (UTRs). In some embodiments, the virally derived, self-amplifying RNA encodes not only the peptides disclosed herein but also the viral replication machinery that enables intracellular RNA amplification and abundant protein expression. In some embodiments, the RNA is directly introduced into the individual. In some embodiments, the RNA is chemically synthesized or transcribed *in vitro*. In some embodiments, the mRNA is produced from a linear DNA template using a T7, a T3, or an Sp6 phage RNA polymerase, and the resulting product contains an open reading frame that encodes the peptides disclosed herein, flanking UTRs, a 5' cap, and a poly(A) tail. In some embodiments, various versions of 5' caps are added during or after the transcription reaction using a vaccinia virus capping enzyme or by incorporating synthetic cap or anti-reverse cap analogues. In some embodiments, an optimal length of the poly(A) tail is added to mRNA either directly from the encoding DNA template or by using poly(A) polymerase. The RNA encodes one or more peptides comprising a fragment that is a T cell epitope capable of binding to at least three HLA class I and/or at least three HLA class II molecules of a patient. In some embodiments, the fragments are derived from an antigen that is expressed in cancer. In some embodiments, the RNA includes signals to enhance stability and translation. In some embodiments, the RNA also includes unnatural nucleotides to increase the half-life or modified nucleosides to change the immunostimulatory profile. In some embodiments, the RNAs is introduced by a needle, a gene gun, an aerosol injector, with patches, via microneedles, by abrasion, among other forms. In some forms the RNA vaccine is incorporated into liposomes or other forms of nanobodies that facilitate cellular uptake of RNA and protect it from degradation. In some embodiments, the RNA vaccine includes a delivery system selected from the group consisting of a transfection agent; protamine; a protamine liposome; a polysaccharide particle; a cationic nanoemulsion; a cationic polymer; a cationic polymer liposome; a cationic nanoparticle; a cationic lipid and cholesterol nanoparticle; a cationic lipid, cholesterol, and PEG nanoparticle; a dendrimer nanoparticle; and/or naked mRNA; naked mRNA with in vivo electroporation; protamine-complexed mRNA; mRNA associated with a positively charged oil-in-water cationic nanoemulsion; mRNA associated with a chemically modified dendrimer and complexed with

polyethylene glycol (PEG)-lipid; protamine-complexed mRNA in a PEG-lipid nanoparticle; mRNA associated with a cationic polymer such as polyethylenimine (PEI); mRNA associated with a cationic polymer such as PEI and a lipid component; mRNA associated with a polysaccharide (for example, chitosan) particle or gel; mRNA in a cationic lipid nanoparticle (for example, 1,2-dioleoyloxy-3-trimethylammoniumpropane (DOTAP) or dioleoylphosphatidylethanolamine (DOPE) lipids); mRNA complexed with cationic lipids and cholesterol; or mRNA complexed with cationic lipids, cholesterol and PEG-lipid. In some embodiments, the RNA vaccine is administered by inhalation or ingestion. In some embodiments, the RNA is introduced into the blood, the thymus, the pancreas, the skin, the muscle, a tumor, or other sites, and/or by an intradermal, intramuscular, subcutaneous, intranasal, intranodal, intravenous, intrasplenic, intratumoral or other delivery route.

Polynucleotide or oligonucleotide components may be naked nucleotide sequences or be in combination with cationic lipids, polymers or targeting systems. They may be delivered by any available technique. For example, the polynucleotide or oligonucleotide may be introduced by needle injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the polynucleotide or oligonucleotide may be delivered directly across the skin using a delivery device such as particle-mediated gene delivery. The polynucleotide or oligonucleotide may be administered topically to the skin, or to mucosal surfaces for example by intranasal, oral, or intrarectal administration.

Uptake of polynucleotide or oligonucleotide constructs may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example, calcium phosphate and DEAE-Dextran and lipofectants, for example, lipofectam and transfectam. The dosage of the polynucleotide or oligonucleotide to be administered can be altered.

Administration is typically in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be, although prophylaxis may be considered therapy), this being sufficient to result in a clinical response or to show clinical benefit to the individual, e.g. an

effective amount to prevent or delay onset of the disease or condition, to ameliorate one or more symptoms, to induce or prolong remission, or to delay relapse or recurrence.

The dose may be determined according to various parameters, especially according to the substance used; the age, weight and condition of the individual to be treated; the route of administration; and the required regimen. The amount of antigen in each dose is selected as an amount which induces an immune response. A physician will be able to determine the required route of administration and dosage for any particular individual. The dose may be provided as a single dose or may be provided as multiple doses, for example taken at regular intervals, for example 2, 3 or 4 doses administered hourly. Typically peptides, polynucleotides or oligonucleotides are typically administered in the range of 1 pg to 1 mg, more typically 1 pg to 10 μg for particle mediated delivery and 1 μg to 1 mg, more typically 1-100 μg, more typically 5-50 μg for other routes. Generally, it is expected that each dose will comprise 0.01-3 mg of antigen. An optimal amount for a particular vaccine can be ascertained by studies involving observation of immune responses in subjects.

Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

In some cases in accordance with the disclosure, more than one peptide or composition of peptides is administered. Two or more pharmaceutical compositions may be administered together/simultaneously and/or at different times or sequentially. Thus, the disclosure includes sets of pharmaceutical compositions and uses thereof. The use of combination of different peptides, optionally targeting different antigens, is important to overcome the challenges of genetic heterogeneity of tumors and HLA heterogeneity of individuals. The use of peptides of the disclosure in combination expands the group of individuals who can experience clinical benefit from vaccination. Multiple pharmaceutical compositions of PEPIs, manufactured for use in one regimen, may define a drug product.

Routes of administration include but are not limited to intranasal, oral, subcutaneous, intradermal, and intramuscular. The subcutaneous administration is particularly preferred.

Subcutaneous administration may for example be by injection into the abdomen, lateral and anterior aspects of upper arm or thigh, scapular area of back, or upper ventrodorsal gluteal area.

The compositions of the disclosure may also be administered in one, or more doses, as well as, by other routes of administration. For example, such other routes include, intracutaneously, intravenously, intravascularly, intraarterially, intraperitnoeally, intrathecally, intratracheally, intracardially, intralobally, intramedullarly, intrapulmonarily, and intravaginally. Depending on the desired duration of the treatment, the compositions according to the disclosure may be administered once or several times, also intermittently, for instance on a monthly basis for several months or years and in different dosages.

Solid dosage forms for oral administration include capsules, tablets, caplets, pills, powders, pellets, and granules. In such solid dosage forms, the active ingredient is ordinarily combined with one or more pharmaceutically acceptable excipients, examples of which are detailed above. Oral preparations may also be administered as aqueous suspensions, elixirs, or syrups. For these, the active ingredient may be combined with various sweetening or flavoring agents, coloring agents, and, if so desired, emulsifying and/or suspending agents, as well as diluents such as water, ethanol, glycerin, and combinations thereof.

One or more compositions of the disclosure may be administered, or the methods and uses for treatment according to the disclosure may be performed, alone or in combination with other pharmacological compositions or treatments, for example chemotherapy and/or immunotherapy and/or vaccine. The other therapeutic compositions or treatments may for example be one or more of those discussed herein, and may be administered either simultaneously or sequentially with (before or after) the composition or treatment of the disclosure.

In some cases the treatment may be administered in combination with checkpoint blockade therapy/checkpopint inhibitors, co-stimulatory antibodies, cytotoxic or non-cytotoxic chemotherapy and/or radiotherapy, targeted therapy or monoclonal antibody therapy. It has been demonstrated that chemotherapy sensitizes tumors to be killed by tumor specific cytotoxic T cells induced by vaccination (Ramakrishnan *et al. J Clin Invest.* 2010; 120(4):1111-1124). Examples

of chemotherapy agents include alkylating agents including nitrogen mustards such as mechlorethamine (HN2), cyclophosphamide, ifosfamide, melphalan (L-sarcolysin) and chlorambucil; anthracyclines; epothilones; nitrosoureas such as carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU) and streptozocin (streptozotocin); triazenes such as decarbazine (DTIC; dimethyltriazenoimidazole-carboxamide; ethylenimines/methylmelamines such as hexamethylmelamine, thiotepa; alkyl sulfonates such as busulfan; Antimetabolites including folic acid analogues such as methotrexate (amethopterin); alkylating agents, antimetabolites, pyrimidine analogs such as fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorodeoxyuridine; FUdR) and cytarabine (cytosine arabinoside); purine analogues and related inhibitors such as mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG) and pentostatin (2'-deoxycoformycin); epipodophylotoxins; enzymes such as L-asparaginase; biological response modifiers such as IFNα, IL-2, G-CSF and GM-CSF; platinum coordination complexes such as cisplatin (cis-DDP), oxaliplatin and carboplatin; anthracenediones such as mitoxantrone and anthracycline; substituted urea such as hydroxyurea; methylhydrazine derivatives including procarbazine (N-methylhydrazine, MIH) and procarbazine; adrenocortical suppressants such as mitotane (o,p'-DDD) and aminoglutethimide; taxol and analogues/derivatives; hormones/hormonal therapy and agonists/antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide, progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate, estrogen such as diethylstilbestrol and ethinyl estradiol equivalents, antiestrogen such as tamoxifen, androgens including testosterone propionate and fluoxymesterone/equivalents, antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide and non-steroidal antiandrogens such as flutamide; natural products including vinca alkaloids such as vinblastine (VLB) and vincristine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin) and mitomycin (mitomycin C), enzymes such as L-asparaginase, and biological response modifiers such as interferon alphenomes.

In some cases the method of treatment is a method of vaccination or a method of providing immunotherapy. As used herein, "immunotherapy" is the treatment of a disease or condition by inducing or enhancing an immune response in an individual. In certain embodiments, immunotherapy refers to a therapy that comprises the administration of one or more drugs to an individual to elicit T cell responses. In a specific embodiment, immunotherapy refers to a therapy that comprises the administration or expression of polypeptides that contain one or more PEPIs to an individual to elicit a T cell response to recognize and kill cells that display the one or more PEPIs on their cell surface in conjunction with a class I HLA. In another specific embodiment, immunotherapy comprises the administration of one or more PEPIs to an individual to elicit a cytotoxic T cell response against cells that display tumor associated antigens (TAAs) or cancer testis antigens (CTAs) comprising the one or more PEPIs on their cell surface. In another embodiment, immunotherapy refers to a therapy that comprises the administration or expression of polypeptides that contain one or more PEPIs presented by class II HLAs to an individual to elicit a T helper response to provide co-stimulation to cytotoxic T cells that recognize and kill diseased cells that display the one or more PEPIs on their cell surface in conjunction with a class I HLAs. In still another specific embodiment, immunotherapy refers to a therapy that comprises administration of one or more drugs to an individual that re-activate existing T cells to kill target cells. The theory is that the cytotoxic T cell response will eliminate the cells displaying the one or more PEPIs, thereby improving the clinical condition of the individual. In some instances, immunotherapy may be used to treat tumors. In other instances, immunotherapy may be used to treat intracellular pathogen-based diseases or disorders.

In some cases the disclosure relates to the treatment of cancer or the treatment of solid tumors. The treatment may be of cancers or malignant or benign tumors of any cell, tissue, or organ type. The cancer may or may not be metastatic. Exemplary cancers include carcinomas, sarcomas, lymphomas, leukemias, germ cell tumors, or blastomas. The cancer may or may not be a hormone related or dependent cancer (*e.g.*, an estrogen or androgen related cancer).

In other cases the disclosure relates to the treatment of a viral, bacterial, fungal or parasitic infection, or any other disease or condition that may be treated by immunotherapy.

Systems

The disclosure provides a system comprising a storage module configured to store data comprising the class I and/or class II HLA genotypes of each subject of a model population of human subjects; and the amino acid sequence of one or more test polypeptides; wherein the model population is representative of a test target human population; and a computation module configured to identify and/or quantify the amino acid sequences in the one or more test polypeptides that are capable of binding to multiple class I HLA molecules of each subject in the model population and/or the amino acid sequences in the one or more test polypeptides that are capable of binding to multiple class II HLA molecules of each subject in the model population. The system may further comprise an output module configured to display any output prediction or treatment selection or recommendation described herein or the value of any pharmodynamic biomarker described herein.

Further embodiments of the disclosure

1. A pharmaceutical composition for treatment of a disease or disorder in a subject of a target human population, comprising one or more polypeptides, each comprising at least a first region and a second region,

(a) the first region being of 10-50 amino acids in length comprising a first amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and

(b) the second region being of 10-50 amino acids in length comprising a second amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population;

wherein the amino acid sequence of the T cell epitope of each of first and second regions comprise different sequences.

2. The pharmaceutical composition of item 1, comprising at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 different polypeptides.

3. The pharmaceutical composition of item 1, comprising 2-40 different polypeptides.

4. The pharmaceutical composition of item 1, wherein the T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population comprises 7 to 11 amino acids, and/or the T cell epitope that binds at least three HLA class II molecules of at least 10% of subjects in the target population comprises 13 to 17 amino acids.

5. The pharmaceutical composition of item 1, wherein the the first region of 10-50 amino acids in length is from an antigen; and the second region of 10-50 amino acids in length is from a same or different antigen.

6. The pharmaceutical composition of item 1, wherein the epitopes of the first and second regions are from a single antigen.

7. The pharmaceutical composition of item 1, wherein the epitopes of the first and second regions are from two or more different antigens.

8. The pharmaceutical composition of item 5, wherein the antigen is a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen.

9. The pharmaceutical composition of item 5, wherein the antigen is selected from the antigens listed in Tables 2 to 7.

10. The pharmaceutical composition of item 6, wherein the two or more different antigens are selected from the antigens listed in Tables 2 to 7 and/or different cancer associated antigens.

11. The pharmaceutical composition of item 9, wherein one or more of the antigens are cancer testis antigens (CTAs).

12. The pharmaceutical composition of item 1, wherein the one or more polypeptides further comprise up to 10 amino acids flanking the T cell epitope that are not part of a consecutive sequence flanking the epitope in a corresponding antigen.

13. The pharmaceutical composition of item 1, wherein the one or more polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the first region and second region and that

(i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

(ii) is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of subjects in the target population; or

(iii) meets both requirements (i) and (ii).

14. The pharmaceutical composition of item 1, wherein the target population is cancer patients and wherein each of the first region and second region comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each T cell epitope,

(i) at least 10% of subjects in the target population express a tumor associated antigen selected from the antigens listed in Table 2 that comprises the T cell epitope; and

(ii) at least 10% of subjects in the target population have at least three HLA class I molecules capable of binding to the T cell epitope;

wherein the T cell epitope of the first and second regions are different from each other.

15. The pharmaceutical composition of item 1, further comprising a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof.

16. The pharmaceutical composition of item 15, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone,

dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

17. A kit comprising, one or more separate containers each container comprising:

(i) one or more polypeptides comprising at least a first region and a second region,

(a) the first region of 10-50 amino acids in length comprising a first amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and

(b) the second region of 10-50 amino acids in length comprising a second amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; wherein the amino acid sequence of the T cell epitope of each of first and second regions comprise different sequences and

(ii) a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof.

18. The kit of item 19, further comprising a package insert.

19. A pharmaceutical composition comprising: one or more nucleic acid molecules expressing one or more polypeptides comprising at least a first region and a second region,

(a) the first region of 10-50 amino acids in length comprising a first amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and

(b) the second region of 10-50 amino acids in length comprising a second amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of

subjects in the target population; wherein the amino acid sequence of the T cell epitope of each of first and second regions comprise different sequences.

20. A method of preparing a polypeptide, or a polynucleic acid that encodes a polypeptide, for use in a method of inducing an immune response in a subject of a target human population, the method comprising:

(i) selecting:

(a) a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and/or by HLA class II genotype; or

(b) one relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and one relevant model human population comprising a plurality of subjects each defined by HLA class II genotype;

(ii) identifying a fragment of up to 50 consecutive amino acids of an antigen that comprises:

(a) a T cell epitope capable, in a high percentage of subjects of the model population selected in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of individual subjects of the model population;

(b) a T cell epitope capable, in a high percentage of subjects of the model population selected in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of individual subjects of the model population; or

(c) a T cell epitope capable, in a high percentage of subjects of the model population selected in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of individual subjects of the model population and a T cell epitope capable, in a high percentage of subjects of the model population selected in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of individual subjects of the model population; and

(iii) preparing a polypeptide, or a polynucleic acid that encodes a polypeptide that comprises one or more fragments identified in step (ii).

21. The method of item 20, further comprising prior to step (iii), selecting a longer fragment of the antigen if the fragment selected in step (ii) is an HLA class I–binding epitope, which longer fragment comprises an amino acid sequence that

(a) comprises the fragment selected in step (ii); and

(b) is an HLA class II molecule-binding T cell epitope capable, in a high percentage of subjects of the model population selected in step (i) that is defined by HLA class II genotype, of binding to at least three, or the most possible HLA class II molecules of individual subjects of the model population.

22. The method of item 20, further comprising prior to step (iii), repeating steps (i) to (ii) to identify on or more additional amino acid sequences of up to 50 consecutive amino acids of the same or a different polypeptide to the first amino acid sequence.

23. A method of inducing an immune response in a subject of a target human population, the method comprising,

administering to the subject a pharmaceutical composition comprising one or more polypeptides comprising at least a first region and a second region,

(a) the first region being of 10-50 amino acids in length comprising a first amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and

(b) the second region being of 10-50 amino acids in length comprising a second amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population;

wherein the amino acid sequence of the T cell epitope of each of first and second regions comprise different sequences.

24. The method of item 23, further comprising prior to the administering step, determining if the subject is likely to have an have a clinical response to administration of a pharmaceutical composition by

(i) assaying a biological sample of the subject to determine HLA genotype of the subject;

(ii) determining that the pharmaceutical composition comprises two or more sequences that are a T cell epitope capable of binding to at least three HLA class I molecules of the subject; and

(iii) determining the probability that a tumor of the subject expresses one or more antigen corresponding to the T cell epitopes identified in step (ii) using population expression data for each antigen, to identify the likelihood of the subject to have a clinical response to administration of the pharmaceutical composition.

25. The method of item 23, wherein the the first region of 10-50 amino acids in length is from an antigen; and the second region of 10-50 amino acids in length is from a same or different antigen.

26. The method of item 23, wherein the epitopes of the first and second regions are from two or more different antigens.

27. The method of item 25, wherein the antigen is a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen.

28. The method of item 23, wherein the T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population comprises 7 to 11 amino acids, and/or the T cell epitope that binds at least three HLA class II molecules of at least 10% of subjects in the target population comprises 13 to 17 amino acids.

29. A pharmaceutical composition for treatment of a disease or disorder in a subject of a target human population, comprising

(a) at least two polypeptides, each of the at least two polypeptides being 10-50 amino acids in length comprising an amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population, and/or at least three HLA class II molecules of at least 10% of subjects in the target population, wherein the amino acid sequence of the T cell epitope of each of the at least two polypeptides are different from each other; and

(b) a pharmaceutically-acceptable adjuvant.

30. The pharmaceutical composition of item 29, comprising at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 different polypeptides.

31. The pharmaceutical composition of item 29, comprising 3-40 different polypeptides.

32. The pharmaceutical composition of item 29, wherein the T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population comprises 7 to 11 amino acids, and/or the T cell epitope that binds at least three HLA class II molecules of at least 10% of subjects in the target population comprises 13 to 17 amino acids.

33. The pharmaceutical composition of item 29, wherein the epitopes of the amino acid sequences of the at least two polypeptides are from a single antigen.

34. The pharmaceutical composition of item 29, wherein the epitopes of the amino acid sequences of the at least two polypeptides are from two or more different antigens.

35. The pharmaceutical composition of item 33, wherein the antigen is a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen.

36. The pharmaceutical composition of item 33, wherein the antigen is selected from the antigens listed in Tables 2 to 7.

37. The pharmaceutical composition of item 34, wherein the two or more different antigens are selected from the antigens listed in Tables 2 to 7 and/or different cancer associated antigens.

38. The pharmaceutical composition of item 37, wherein one or more of the antigens are cancer testis antigens (CTAs).

39. The pharmaceutical composition of item 29, wherein each of the at least two polypeptides being 10-50 amino acids in length is from an antigen a same or different antigen.

40. The pharmaceutical composition of item 29, wherein the at least two different polypeptides further comprise up to 10 amino acids flanking the T cell epitope that are not part of a consecutive sequence flanking the epitope in a corresponding antigen.

41. The pharmaceutical composition of item 29, wherein two of the at least two polypeptides are arranged end to end or overlapping in a joined polypeptide.

42. The pharmaceutical composition of item 41, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other.

43. The pharmaceutical composition of item 42, wherein the joined polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the two polypeptides and that

(i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

(ii) is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of subjects in the target population; or

(iii) meets both requirements (i) and (ii).

44. The pharmaceutical composition of item 29, wherein the target population is cancer patients and wherein each polypeptide comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each T cell epitope,

(i) at least 10% of subjects in the target population express a tumor associated antigen selected from the antigens listed in Table 2 that comprises the T cell epitope; and

(ii) at least 10% of subjects in the target population have at least three HLA class I molecules capable of binding to the T cell epitope;

wherein the T cell epitope of the at least two polypeptides are different from each other.

45. The pharmaceutical composition of item 29, further comprising a pharmaceutically acceptable diluent, carrier, preservative, or combination thereof.

46. The pharmaceutical composition of item 29, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

47. A pharmaceutical composition for treatment of a disease or disorder in a subject of a target human population, comprising

(a) a polypeptide of 10-50 amino acids in length and comprising a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and

(b) a pharmaceutically-acceptable adjuvant.

48. The pharmaceutical composition of item 47, comprising at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 different polypeptides, each of the different polypeptides being 10-50 amino acids in length comprising a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the

target population, wherein the amino acid sequence of the T cell epitope of each of the different polypeptides are different from each other.

49. The pharmaceutical composition of item 48, comprising 2-40 different polypeptides.

50. The pharmaceutical composition of item 47, wherein the T cell epitope that binds at least three HLA class I molecules of the subject comprises 7 to 11 amino acids, and/or the T cell epitope that binds at least three HLA class II molecules comprises 13 to 17 amino acids.

51. The pharmaceutical composition of item 48, comprising at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are from a single antigen.

52. The pharmaceutical composition of item 48, comprising at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are from two or more different antigens.

53. The pharmaceutical composition of item 51, wherein the antigen is an antigen expressed by a cancer cell, a neoantigen expressed by a cancer cell, a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen.

54. The human subject-specific pharmaceutical composition of item 51, wherein the antigen is selected from the antigens listed in Tables 2 to 7.

55. The human subject-specific pharmaceutical composition of item 51, comprising at least two different polypeptides, wherein two of the polypeptides are arranged end to end or overlapping in a joined polypeptide.

56. The human subject-specific pharmaceutical composition of item 47, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone,

dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

57. The human subject-specific pharmaceutical composition of item 47, comprising at least two different polypeptides, wherein two of the at least two polypeptides are arranged end to end or overlapping in a joined polypeptide.

58. The human subject-specific pharmaceutical composition of item 57, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other.

59. The human subject-specific pharmaceutical composition of item 58, wherein the joined polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the two polypeptides and that
(i) corresponds to a fragment of a human polypeptide expressed in healthy cells of the subject;
(ii) is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or
(iii) meets both requirements (i) and (ii).

60. The human subject-specific pharmaceutical composition of item 48, wherein the at least two polypeptides do not comprise any amino acid sequences that
(i) correspond to a fragment of a human polypeptide expressed in healthy cells; or
(ii) correspond to a fragment of a human polypeptide expressed in healthy cells and is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

61. A method of identifying and treating a subject of a target population of cancer patients who will likely have a clinical response to administration of a pharmaceutical composition according to item 1, the method comprising,

(i) assaying a biological sample of the subject to determine HLA genotype of the subject;
(ii) determining that the pharmaceutical composition comprises two or more sequences that are a T cell epitope capable of binding to at least three HLA class I molecules of the subject;
(iii) determining the probability that a tumor of the subject expresses one or more antigen corresponding to the T cell epitopes identified in step (ii) using population expression data for each antigen, to identify the likelihood of the subject to have a clinical response to administration of the pharmaceutical composition; and
(iv) administering the composition of item 1 to the identified subject.

62. The method of item 61, further comprising prior to the administering step
assaying a tumor sample from the subject to determine that the three or more peptides of the pharmaceutical composition comprise two or more different amino acid sequences each of which is

a. a fragment of a cancer-associated antigen expressed by cancer cells of the subject as determined in step (i); and
b. a T cell epitope capable of binding to at least three HLA class I molecules of the subject; and

confirming the subject as likely to have a clinical response to the method of treatment.

63. The method of item 61, wherein the composition comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 different polypeptides.

64. The method of item 61, wherein the composition comprises 2-40 different polypeptides.

65. The method of item 61, wherein the T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population comprises 7 to 11 amino acids, and/or the T cell epitope that binds at least three HLA class II molecules of at least 10% of subjects in the target population comprises 13 to 17 amino acids.

66. The method of item 61, wherein the the first region of 10-50 amino acids in length is from an antigen; and the second region of 10-50 amino acids in length is from a same or different antigen.

67. The method of item 61, wherein the epitopes of the first and second regions are from a single antigen.

68. The method of item 61, wherein the epitopes of the first and second regions are from two or more different antigens.

69. The method of item 67, wherein the antigen is a cancer-associated antigen or a tumor-associated antigen.

70. The method of item 67, wherein the antigen is selected from the antigens listed in Table 2.

71. The method of item 67, wherein the two or more different antigens are selected from the antigens listed in Table 2 and/or different cancer associated antigens.

72. The method of item 71, wherein one or more of the antigens are cancer testis antigens (CTAs).

73. The method of item 61, wherein the one or more polypeptides further comprise up to 10 amino acids flanking the T cell epitope that are not part of a consecutive sequence flanking the epitope in a corresponding antigen.

74. The method of item 61, wherein the one or more polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the first region and second region and that

(i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

(ii) is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of subjects in the target population; or

(iii) meets both requirements (i) and (ii).

75. The method of item 61, wherein the target population is cancer patients and wherein each of the first region and second region comprises an amino acid sequence that is an HLA class I-binding T cell epitope, and wherein for each T cell epitope,

(iii) at least 10% of subjects in the target population express a tumor associated antigen selected from the antigens listed in Table 2 that comprises the T cell epitope; and

(iv) at least 10% of subjects in the target population have at least three HLA class I molecules capable of binding to the T cell epitope;

wherein the T cell epitope of the first and second regions are different from each other.

76. The method of item 61, wherein the composition further comprises a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof.

77. The method of item 61, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

78. A kit comprising:

(a) a first composition comprising (i) a first polypeptide of 10-50 amino acids in length and comprising a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and (ii) a pharmaceutically-acceptable adjuvant;

(b) a second composition comprising (i) a second polypeptide of 10-50 amino acids in length and comprising a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population; and (ii) a pharmaceutically-acceptable adjuvant,

wherein the first and second polypeptides comprise different T cell epitopes.

79. The kit of item 78, wherein the first composition and/or the second composition comprise one or more additional polypeptides, wherein each additional polypeptide being of 10-50 amino acids in length comprising an amino acid sequence that is a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population, wherein the amino acid sequences comprise different T cell epitopes.

80. A method of identifying and treating a subject of a target population of cancer patients who will likely have an immune response to administration of a pharmaceutical composition according to item 1, the method comprising,

(i) assaying a biological sample of the subject to determine HLA genotype of the subject;

(ii) determining that the pharmaceutical composition comprises two or more sequences that are a T cell epitope capable of binding to at least three HLA class I molecules of the subject;

(iii) administering the composition of item 1 to the identified subject.

81. A pharmaceutical composition comprising: a nucleic acid molecule expressing two or more polypeptides, each polypeptide being 10-50 amino acids in length comprising a T cell epitope that binds at least three HLA class I molecules of at least 10% of subjects in the target population and/or at least three HLA class II molecules of at least 10% of subjects in the target population, wherein each of the two or more polypeptides comprises a different T cell epitope, wherein the polypeptides do not comprise amino acid sequences that are adjacent to each other in a corresponding antigen.

Examples

Example 1 – HLA-epitope binding prediction process and validation

Predicted binding between particular HLA and epitopes (9 mer peptides) was based on the Immune Epitope Database tool for epitope prediction (www.iedb.org).

The HLA I-epitope binding prediction process was validated by comparison with HLA I-epitope pairs determined by laboratory experiments. A dataset was compiled of HLA I-epitope pairs reported in peer reviewed publications or public immunological databases.

The rate of agreement with the experimentally determined dataset (Table 9) was determined. The binding HLA I-epitope pairs of the dataset were correctly predicted with a 93% probability. Coincidentally the non-binding HLA I-epitope pairs were also correctly predicted with a 93% probability.

Table 9. Analytical specificity and sensitivity of the HLA-epitope binding prediction process.

HLA-epitope pairs	*True epitopes (n=327)* *(Binder match)*	*False epitopes (n=100)* *(Non-binder match)*
HIV	91% (32)	82% (14)
Viral	100% (35)	100% (11)
Tumor	90% (172)	94% (32)
Other (fungi, bacteria, etc.)	100% (65)	95% (36)
All	*93% (304)*	*93% (93)*

The accuracy of the prediction of multiple HLA binding epitopes was determined. Based on the analytical specificity and sensitivity using the 93% probability for both true positive and true negative prediction and 7% (=100% - 93%) probability for false positive and false negative prediction, the probability of the existence of a multiple HLA binding epitope in a person can be calculated. The probability of multiple HLA binding to an epitope shows the relationship between the number of HLAs binding an epitope and the expected minimum number of real

binding. Per PEPI definition three is the expected minimum number of HLA to bind an epitope (bold).

Table 10. Accuracy of multiple HLA binding epitopes predictions.

Expected minimum number of real HLA binding	Predicted number of HLAs binding to an epitope						
	0	1	2	3	4	5	6
1	35%	95%	100%	100%	100%	100%	100%
2	6%	29%	90%	99%	100%	100%	100%
3	1%	4%	22%	84%	98%	100%	100%
4	0%	0%	2%	16%	78%	96%	99%
5	0%	0%	0%	1%	10%	71%	94%
6	0%	0%	0%	0%	0%	5%	65%

The validated HLA-epitope binding prediction process was used to determine all HLA-epitope binding pairs described in the Examples below.

Example 2 – Epitope presentation by multiple HLA predicts cytotoxic T lymphocyte (CTL) response

The presentation of one or more epitopes of a polypeptide antigen by one or more HLA I of an individual is predictive for a CTL response was determined.

The study was carried out by retrospective analysis of six clinical trials, conducted on 71 cancer and 9 HIV-infected patients (Table 11)[1-7]. Patients from these studies were treated with an HPV vaccine, three different NY-ESO-1 specific cancer vaccines, one HIV-1 vaccine and a CTLA-4 specific monoclonal antibody (Ipilimumab) that was shown to reactivate CTLs against NY-ESO-1 antigen in melanoma patients. All of these clinical trials measured antigen specific CD8+ CTL responses (immunogenicity) in the study subjects after vaccination. In some cases, correlation between CTL responses and clinical responses were reported.

No patient was excluded from the retroactive study for any reason other than data availability. The 157 patient datasets (Table 11) were randomized with a standard random number generator to create two independent cohorts for training and evaluation studies. In some

cases the cohorts contained multiple datasets from the same patient, resulting in a training cohort of 76 datasets from 48 patients and a test/validation cohort of 81 datasets from 51 patients.

Table 11. Summary of patient datasets

Clinical trial	Immunotherapy	Target Antigen	Disease	# Patients*	# Data sets (#antigen x #patient)	Immunoassay performed in the clinical trials**	HLA genotyping method	Ref
1	VGX-3100	HPV16-E6 HPV16-E7 HPV18-E6 HPV18-E7 HPV16/18	Cervical cancer	17/18	5 x 17	IFN-γ ELISPOT	High Resolution SBT	1
2	HIVIS vaccine	HIV-1 Gag HIV-1 RT	AIDS	9/12	2 x 9	IFN-γ ELISPOT	Low-Medium Resolution SSO	2
3	rNY-ESO-1	NY-ESO-1	Breast-and ovarian cancers, melanoma and sarcoma	18/18	1 x 18	In vitro and Ex vivo IFN-γ ELISPOT	High Resolution SBT	3 4
4	Ipilimumab	NY-ESO-1	Metastatic melanoma	19/20	1 x 19	ICS after T-cell stimulation	Low to medium resolution typing, SSP of genomic DNA, high resolution sequencing	5
5	NY-ESO-1f	NY-ESO-1 (91-110)	Esophageal-, non-small-cell lung- and gastric cancer	10/10	1 x 10	ICS after T-cell stimulation	SSO probing and SSP of genomic DNA	6
6	NY-ESO-1 overlapping peptides	NY-ESO-1 (79-173)	Esophageal- and lung cancer, malignant melanoma	7/9	1 x 7	ICS after T-cell stimulation	SSO probing and SSP of genomic DNA	7
Total	6	7		80	157	N/A		

*Number of patients used in the retrospective analysis from the original number of patient of the clinical trials.
**Immunoassays are based on T cell stimulation with antigen-specific peptide pools and quantify the released cytokines by different techniques.
CT: Clinical trial; SBT: Sequence Based Typing; SSO: Sequence-Specific Oligonucleotide; ICS: Intracellular cytokine staining; SSP: Sequence-specific priming

The reported CTL responses of the training dataset were compared with the HLA I restriction profile of epitopes (9 mers) of the vaccine antigens. The antigen sequences and the HLA I genotype of each patient were obtained from publicly available protein sequence databases or peer reviewed publications and the HLA I-epitope binding prediction process was blinded to patients' clinical CTL response data. The number of epitopes from each antigen predicted to bind to at least 1 (PEPI1+), or at least 2 (PEPI2+), or at least 3 (PEPI3+), or at least 4 (PEPI4+), or at least 5 (PEPI5+), or all 6 (PEPI6) HLA class I molecules of each patient was determined and the number of HLA bound were used as classifiers for the reported CTL responses. The true positive rate (sensitivity) and true negative rate (specificity) were determined from the training dataset for each classifier (number of HLA bound) separately.

ROC analysis was performed for each classifier. In a ROC curve, the true positive rate (Sensitivity) was plotted in function of the false positive rate (1-Specificity) for different cut-off points (FIG. 1). Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold (epitope (PEPI) count). The area under the ROC curve (AUC) is a measure of how well the classifier can distinguish between two diagnostic groups (CTL responder or non-responder).

The analysis unexpectedly revealed that predicted epitope presentation by multiple class I HLAs of a subject (PEPI2+, PEPI3+, PEPI4+, PEPI5+, or PEPI6), was in every case a better predictor of CTL response than epitope presentation by merely one or more HLA class I (PEPI1+, AUC = 0.48, Table 12).

Table 12. Determination of diagnostic value of the PEPI biomarker by ROC analysis

Classifiers	AUC

PEPI1+	0.48
PEPI2+	0.51
PEPI3+	0.65
PEPI4+	0.52
PEPI5+	0.5
PEPI6+	0.5

The CTL response of an individual was best predicted by considering the epitopes of an antigen that could be presented by at least 3 HLA class I of an individual (PEPI3+, AUC = 0.65, Table 12). The threshold count of PEPI3+ (number of antigen-specific epitopes presented by 3 or more HLA of an individual) that best predicted a positive CTL response was 1 (Table 13). In other words, at least one antigen-derived epitope is presented by at least 3 HLA class I of a subject (≥1 PEPI3+), then the antigen can trigger at least one CTL clone, and the subject is a likely CTL responder. Using the ≥1 PEPI3+ threshold to predict likely CTL responders ("≥1 PEPI3+ Test") provided 76% diagnostic sensitivity (Table 13).

Table 13. Determination of the ≥1 PEPI3+ threshold to predict likely CTL responders in the training dataset.

	PEPI3+ Count											
	1	2	3	4	5	6	7	8	9	10	11	12
Sensitivity:	**0.76**	0.60	0.31	0.26	0.14	0.02	0	0	0	0	0	0
1-Specificity:	**0.59**	0.24	0.21	0.15	0.09	0.06	0.06	0.03	0.03	0.03	0.03	0.03

Example 3 – Validation of the ≥1 PEPI3+ Test

The test cohort of 81 datasets from 51 patients was used to validate the ≥1 PEPI3+ threshold to predict an antigen-specific CTL response. For each dataset in the test cohort it was determined whether the ≥1 PEPI3+ threshold was met (at least one antigen-derived epitope

presented by at least three class I HLA of the individual). This was compared with the experimentally determined CTL responses reported from the clinical trials (Table 14).

The clinical validation demonstrated that a PEPI3+ peptide induce CTL response in an individual with 84% probability. 84% is the same value that was determined in the analytical validation of the PEPI3+ prediction, epitopes that binds to at least 3 HLAs of an individual (Table 10). These data provide strong evidences that immune responses are induced by PEPIs in individuals.

Table 14. Diagnostic performance characteristics of the ≥1 PEPI3+ Test (n=81).

Performance characteristic		Description	Result
Positive predictive value (PPV)	100%[A/(A + B)]	The likelihood that an individual that meets the ≥1 PEPI3+ threshold has antigen-specific CTL responses after treatment with immunotherapy.	*84%*
Sensitivity	100%[A / (A+C)]	The proportion of subjects with antigen-specific CTL responses after treatment with immunotherapy who meet the ≥1 PEPI3+ threshold.	*75%*
Specificity	100%[D / (B + D)]	The proportion of subjects without antigen-specific CTL responses after treatment with immunotherapy who do not meet the ≥1 PEPI3+ threshold.	*55%*
Negative predictive value (NPV)	100%[D/(C +D)]	The likelihood that an individual who does not meet the ≥1 PEPI3+ threshold does not have antigen-specific CTL responses after treatment with immunotherapy.	*42%*
Overall percent agreement (OPA)	100%[(A + D)/ N]	The percentage of predictions based on the ≥1 PEPI3+ threshold that match the experimentally determined result, whether positive or negative.	*70%*
Fisher's exact (p)			*0.01*

ROC analysis determined the diagnostic accuracy, using the PEPI3+ count as cut-off values (Fig. 2). The AUC value = 0.73. For ROC analysis an AUC of 0.7 to 0.8 is generally considered as fair diagnostic.

A PEPI3+ count of at least 1 (≥1 PEPI3+) best predicted a CTL response in the test dataset (Table 15). This result confirmed the threshold determined during the training (Table 12).

Table 15. Confirmation of the ≥1 PEPI3+ threshold to predict likely CTL responders in the test/validation dataset.

	PEPI3+ Count											
	1	2	3	4	5	6	7	8	9	10	11	12
Sensitivity:	**0.75**	0.52	0.26	0.23	0.15	0.13	0.08	0.05	0	0	0	0
1-Specificity:	**0.45**	0.15	0.05	0	0	0	0	0	0	0	0	0

Example 4 – The ≥1 PEPI3+ Test predicts CD8+ CTL reactivities

The ≥1 PEPI3+ Test was compared with a previously reported method for predicting a specific human subject's CTL response to peptide antigens.

The HLA genotypes of 28 cervical cancer and VIN-3 patients that received the HPV-16 synthetic long peptide vaccine (LPV) in two different clinical trials were determined from DNA samples[8 9 10]. The LPV consists of long peptides covering the HPV-16 viral oncoproteins E6 and E7. The amino acid sequence of the LPV was obtained from these publications. The publications also report the T cell responses of each vaccinated patient to pools of overlapping peptides of the vaccine.

For each patient epitopes (9 mers) of the LPV that are presented by at least three patient class I HLA (PEPI3+s) were identified and determined their distribution among the peptide pools was determined. Peptides that comprised at least one PEPI3+ (≥1 PEPI3+) were predicted to induce a CTL response. Peptides that comprised no PEPI3+ were predicted not to induce a CTL response.

The ≥1 PEPI3+ Test correctly predicted 489 out of 512 negative CTL responses and 8 out of 40 positive CTL responses measured after vaccination (Fig. 3A). Overall, the agreement

between the ≥1 PEPI3+ Test and experimentally determined CD8+ T cell reactivity was 90% ($p<0.001$).

For each patient the distribution among the peptide pools of epitopes that are presented by at least one patient class I HLA (≥1 PEPI1+, HLA restricted epitope prediction, prior art method) was also determined. ≥1 PEPI1+ correctly predicted 116 out of 512 negative CTL responses and 37 out of 40 positive CTL responses measured after vaccination (FIG. 3B). Overall, the agreement between the HLA restricted epitope prediction (≥1 PEPI1+) and CD8+ T cell reactivity was 28% (not significant).

Example 5 - Prediction of HLA class II restricted CD4+ helper T cell epitopes

The 28 cervical cancer and VIN-3 patients that received the HPV-16 synthetic long peptide vaccine (LPV) in two different clinical trials (as detailed in Example 4) were investigated for CD4+ T helper responses following LPV vaccination (FIG. 4). The sensitivity of the prediction of HLA class II restricted epitopes was 78%, since the State of Art tool predicted 84 positive responses (positive CD4+ T cell reactivity to a peptide pool for a person's DP alleles) out of 107 (sensitivity = 78%). The specificity was 22% since it could rule out 7 negative responses out of 31. Overall, the agreement between HLA-restricted class II epitope prediction and CD4+ T cell reactivity was 66%, which was statistically not significant.

Example 6 - The ≥1 PEPI3+ Test predicts T cell responses to full length LPV polypeptides

Using the same reported studies as Examples 4 and 5, the ≥1 PEPI3+ Test was used to predict patient CD8+ and CD4+ T cell responses to the full length E6 and E7 polypeptide antigens of the LPV vaccine. Results were compared to the experimentally determined responses were reported. The Test correctly predicted the CD8+ T cell reactivity (PEPI3+) of 11 out of 15 VIN-3 patients with positive CD8+ T cell reactivity test results (sensitivity 73%, PPV 85%) and of 2 out of 5 cervical cancer patients (sensitivity 40%, PPV 100%). The CD4+ T cell reactivities (PEPI4+) were correctly predicted 100% both of VIN-3 and cervical cancer patients (Fig 5).

Class I and class II HLA restricted PEPI3+ count was also observed to correlate with the reported clinical benefit to LPV vaccinated patients. Patients with higher PEPI3+ counts had either complete or partial response already after 3 months.

Example 7 – Case Study

pGX3001 is an HPV16 based DNA vaccine containing full length E6 and E7 antigens with a linker in between. pGX3002 is an HPV18 based DNA vaccine containing full length E6 and E7 antigens with a linker in between. A Phase II clinical trial investigated the T cell responses of 17 HPV-infected patients with cervical cancer who were vaccinated with both pGX3001 and pGX3002 (VGX-3100 vaccination)[1].

Fig. 5-6 shows for two illustrative patients (patient 12-11 and patient 14-5) the position of each epitope (9 mer) presented by at least 1 (PEPI1+), at least 2 (PEPI2+), at least 3 (PEPI3+), at least 4 (PEPI4+), at least 5 (PEPI5+), or all 6 (PEPI6) class I HLA of these patients within the full length sequence of the two HPV-16 and two HPV-18 antigens.

Patient 12-11 had an overall PEPI1+ count of 54 for the combined vaccines (54 epitopes presented by one or more class I HLA). Patient 14-5 had a PEPI1+ count of 91. Therefore patient 14-5 has a higher PEPI1+ count than patient 12-11 with respect to the four HPV antigens. The PEPI1+s represent the distinct vaccine antigen specific HLA restricted epitope sets of patients 12-11 and 14-5. Only 27 PEPI1+s were common between these two patients.

For the PEPI3+ counts (number of epitopes presented by three or more patient class I HLA), the results for patients 12-11 and 14-5 were reversed. Patient 12-11 had a PEPI3+ count of 8, including at least one PEPI3+ in each of the four HPV16/18 antigens. Patient 14-5 had a PEPI3+ count of 0.

The reported immune responses of these two patients matched the PEPI3+ counts, not the PEPI1+ counts. Patient 12-11 developed immune responses to each of the four antigens post-vaccination as measured by ELISpot, whilst patient 14-5 did not develop immune responses to any of the four antigens of the vaccines. A similar pattern was observed when the PEPI1+ and PEPI3+ sets of all 17 patients in the trial were compared. There was no correlation between the

PEPI1+ count and the experimentally determined T cell responses reported from the clinical trial. However, we correlation between the T cell immunity predicted by the ≥1 PEPI3+ Test and the reported T cell immunity was observed. The ≥1 PEPI3+ Test predicted the immune responders to HPV DNA vaccine.

Moreover, the diversity of the patient's PEPI3+ set resembled the diversity of T cell responses generally found in cancer vaccine trials. Patients 12-3 and 12-6, similar to patient 14-5, did not have PEPI3+s predicting that the HPV vaccine could not trigger T cell immunity. All other patients had at least one PEPI3 predicting the likelihood that the HPV vaccine can trigger T cell immunity. 11 patients had multiple PEPI3+ predicting that the HPV vaccine likely triggers polyclonal T cell responses. Patients 15-2 and 15-3 could mount high magnitude T cell immunity to E6 of both HPV, but poor immunity to E7. Other patients 15-1 and 12-11 had the same magnitude response to E7 of HPV18 and HPV16, respectively.

Example 8 – Design of a Model Population for conducting *in silico* trials and identifying candidate precision vaccine targets for large population

An *in silico* human trial cohort of 433 subjects with complete 4-digit HLA class I genotype (2 x HLA-A*xx:xx; 2 x HLA-B*xx:xx; 2 x HLA-C*xx:xx) and demographic information was compiled. This Model Population has subjects with mixed ethnicity having a total of 152 different HLA alleles that are representative for >85% of presently known allele G-groups.

A database of a "Big Population" containing 7,189 subjects characterized with 4-digit HLA genotype and demographic information was also established. The Big Population has 328 different HLA class I alleles. The HLA allele distribution of the Model Population significantly correlated with the Big Population (Table 16) (Pearson p<.001). Therefore the 433 patient Model Population is representative for a 16 times larger population.

The Model Population is representative for 85% of the human race as given by HLA diversity as well as HLA frequency.

Table 16. Statistical analysis of HLA distributions in "Model Population" vs. "Big Population".

Group name 1	Group name 2	Pearson R value	Correlation	P Value
433 Model Population	7,189 Big Population	0.89	Strong	P<0.001

Example 9 –*In silico* trials based on the identification of multiple HLA binding epitopes predict the reported T cell response rates of clinical trials

The objective of this study was to determine whether a model population, such as the one described in Example 8, may be used to predict CTL reactivity rates of vaccines, i.e. used in an *in silico* efficacy trials.

Twelve peptide vaccines derived from cancer antigens that induced T cell responses in a subpopulation of subjects were identified from peer reviewed publications. These peptides have been investigated in clinical trials enrolling a total of 172 patients (4 ethnicities). T cell responses induced by the vaccine peptides have been determined from blood specimens and reported. The immune response rate as the percentage of study subjects with positive T cell responses measured in the clinical trials was determined (FIG. 7).

Table 17. Clinical trials conducted with peptide vaccines.

Peptide vaccines	*Source antigen*	*Peptide length*	*T cell assay*	*Pop. (n)*	*Ethnicity*	*Ref.*
MMNLMQPKTQQTYTYD	JUP	16mer	Multimer staining	18	Canadian	[12]
GRGSTTTNYLLDRDDYRNTSD	ADA17	21mer	Multimer staining	18	Canadian	[12]
LKKGAADGGKLDGNAKLNRSLK	BAP31	22mer	Multimer staining	18	Canadian	[12]

FPPKDDHTLKFLYDDNQRPYPP	TOP2A	22mer	Multimer staining	18	Canadian	[12]
RYRKPDYTLDDGHGLLRFKST	Abl-2	21mer	Multimer staining	18	Canadian	[12]
QRPPFSQLHRFLADALNT	DDR1	18mer	Multimer staining	18	Canadian	[12]
ALDQCKTSCALMQQHYDQTSCFSSP	ITGB8	25mer	Multimer staining	18	Canadian	[12]
STAPPAHGVTSAPDTRPAPGSTAPP	MUC-1	25mer	Proliferation	80	Canadian	[13]
YLEPGPVTA	gp100	9mer	Tetramer	18	US	[14]
MTPGTQSPFFLLLLLTVLTVV	MUC-1	21mer	Cytotoxicity	10	Israeli	[15]
SSKALQRPV	Bcr-Abl	9mer	ELISPOT	4	US	[16]
RMFPNAPYL	WT-1	9mer	Multimer staining	24	US	[17]
RMFPNAPYL (HLA-A*0201)	WT-1	9mer	Cytokine staining	18	CEU	[18]

The 12 peptides were investigated with the ≥1 PEPI3+ Test in each of the 433 subjects of the Model Population described in Example 8. The "≥1 PEPI3+ Score" for each peptide was calculated as the proportion of subjects in the Model Population having at least one vaccine derived epitope that could bind to at least three subject-specific HLA class I (≥1 PEPI3+). If the corresponding clinical trial stratified patients for HLA allele selected population, the Model Population was also filtered for subjects with the respective allele(s) (Example: WT1, HLA-A*0201).

The experimentally determined response rates reported from the trials were compared with the ≥1 PEPI3+ Scores. The Overall Percentage of Agreements (OPA) were calculated on the paired data (Table 18). A linear correlation between ≥1 PEPI3+ Score and response rate (R^2 =

0.77) was observed (FIG. 7). This result shows that the identification of peptides predicted to bind to multiple HLAs of an individual is useful to predict *in silico* the outcome of clinical trials.

Table 19. Comparison of ≥1 PEPI3+ Scores and CTL response rates of 12 peptide vaccines.

Peptide vaccine	*Source antigen*	*Response rate (Clinical Trials)*	*≥1 PEPI3+ Score* (Model Population)*	*OPA*
MMNLMQPKTQQTYTYD	JUP	0%	22%	NA
GRGSTTTNYLLDRDDYRNTSD	ADA17	11%	18%	61%
LKKGAADGGKLDGNAKLNRSLK	BAP31	11%	7%	64%
FPPKDDHTLKFLYDDNQRPYPP	TOP2A	11%	39%	28%
RYRKPDYTLDDGHGLLRFKST	Abl-2	17%	12%	71%
QRPPFSQLHRFLADALNT	DDR1	17%	5%	29%
ALDQCKTSCALMQQHYDQTSCFSSP	ITGB8	28%	31%	90%
STAPPAHGVTSAPDTRPAPGSTAPP	MUC-1	20%	2%	10%
YLEPGPVTA	gp100	28%	4%	14%
MTPGTQSPFFLLLLLTVLTVV	MUC-1	90%	95%	95%
SSKALQRPV	Bcr-Abl	0%	0%	100%
RMFPNAPYL	WT-1	100%	78%	78%
RMFPNAPYL (HLA-A*0201)	WT-1	81%	61%	75%

** % subjects in the Model Population with ≧1 vaccine derived PEPI3+*

Example 10. *In silico* trials based on the identification of multiple HLA binding epitopes predict the reported T cell response rates of clinical trials II

Nineteen clinical trials with published immune response rates (IRR) conducted with peptide or DNA based vaccines were identified (Table 19). These trials involved 604 patients (9 ethnicities) and covered 38 vaccines derived from tumor and viral antigens. Vaccine antigen specific CTL responses were measured in each study patient and the response rate in the clinical study populations was calculated and reported.

Each vaccine peptide of the 19 clinical trials was investigated with the ≥1 PEPI3+ Test in each subject of the Model Population. The ≥1 PEPI3+ Score for each peptide was calculated as the proportion of subjects in the Model Population having at least one vaccine derived PEPI3+. The experimentally determined response rates reported from the trials were compared with the PEPI Scores, as in Example 9 (Table 20). A linear correlation between the response rate and ≥1 PEPI3+ Score ($R^2 = 0.70$) was observed (FIG. 8). This result confirms that the identification of peptides predicted to bind to multiple HLAs of an individual can predict T cell responses of subjects, and *in silico* trials can predict the outcome of clinical trials.

Table 20. Response rates published in clinical trials.

Immunotherapy	Type	CTL assay	Pop. (n)	Race/ Ethnicity	Ref.
StimuVax	peptide	Proliferation	80	Canadian	13
gp100 vaccine	DNA	Tetramer	18	US	14
IMA901 phase I	peptide	ELISPOT	64	CEU	19
IMA901 phase II	peptide	Multimer staining	27	CEU	
ICT107	peptide	ICC	15	US	20
ProstVac	DNA	ELISPOT	32	CEU87%, Afr. Am.12%, Hisp.1%	21
Synchrotope TA2M	DNA	Tetramer	26	US	22
MELITAC 12.1	peptide	ELISPOT	167	US	23
WT1 vaccine	peptide	Tetramer	22	Japanese	24

Ipilimumab (NY-ESO-1)	checkpoint inhibitor **	ICC	19	US	5
VGX-3100	DNA	ELISPOT	17	US	1
HIVIS-1	DNA	ELISPOT	12	CEU98%, Asian1%, Hisp.1%	2
ImMucin	peptide	Cytotoxicity	10	Israeli	15
NY-ESO-1 OLP	peptide	IFN-gamma	7	Japanese	7
GVX301	peptide	Proliferation	14	CEU	25
WT1 vaccine	peptide	ELISPOT	12	US	26
WT1 vaccine	peptide	ICC	18	CEU	18
DPX-0907*	peptide	Multimer staining	18	Canadian	12
Melanoma peptide vaccine	peptide	ELISPOT	26	White	27

Table 21. Linear correlation between PEPI Score and response rate ($R^2 = 0.7$).

Immunotherapy	Clinical Trial Response Rate	≥1 PEPI3+ Score*	OPA
StimuVax (failed to show efficacy in Phase III)	20%	2%	10%
gp100 vaccine	28%	4%	14%
IMA901 phase I	74%	48%	65%
IMA901 phase II	64%	48%	75%
ICT107	33%	52%	63%
ProstVac	45%	56%	80%
Synchrotope TA2M	46%	24%	52%
MELITAC 12.1	49%	47%	96%
WT1 vaccine	59%	78%	76%
Ipilimumab (NY-ESO-1*)	72%	84%	86%

VGX-3100	78%	87%	90%
HIVIS-1	80%	93%	86%
ImMucin	90%	95%	95%
NY-ESO-1 OLP	100%	84%	84%
GVX301	64%	65%	98%
WT1 vaccine	83%	80%	96%
WT1 vaccine	81%	61%	75%
DPX-0907	61%	58%	95%
Melanoma peptide vaccine	52%	42%	81%

** % subjects in the Model Population with ≧1 vaccine derived PEPI3+*

Example 11 – *In silico* trial based on the identification of multiple HLA binding epitopes in a multi-peptide vaccine predict the reported clinical trial immune response rate

IMA901 is a therapeutic vaccine for renal cell cancer (RCC) comprising 9 peptides derived from tumor-associated peptides (TUMAPs) that are naturally presented in human cancer tissue. A total of 96 HLA-A*02+ subjects with advanced RCC were treated with IMA901 in two independent clinical studies (phase I and phase II). Each of the 9 peptides of IMA901 have been identified in the prior art as HLA-A2-restricted epitopes. Based on currently accepted standards, they are all strong candidate peptides to boost T cell responses against renal cancer in the trial subjects, because their presence has been detected in renal cancer patients, and because the trial patients were specifically selected to have at least one HLA molecule capable of presenting each of the peptides.

For each subject in the Model population how many of the nine peptides of the IMA901 vaccine were capable of binding to three or more HLA was determined. Since each peptide in the IMA901 vaccine is a 9 mer this corresponds to the PEPI3+ count. The results were compared with the immune response rates reported for the Phase I and Phase II clinical trials (Table 22).

Table 22. Immune Response Rates in the Model Population and in two clinical trials to IMA901

Immune responses to TUMAPs	Model Population (HLA-A2+)	Phase I (n=27)*	Phase II (n=64)*

	(n=180)		
No peptide	39%	25%	36%
1 peptide	34%	44%	38%
≧ 2 peptides	27% (MultiPEPI Score)	29%	26%
≧ 3 peptides	3%	ND	3%

**No of patients evaluated for immune responses*

The phase I and phase II study results show the variability of the immune responses to the same vaccine in different trial cohorts. Overall, however, there was a good agreement between response rates predicted by the ≥2 PEPI3+ Test and the reported clinical response rates.

In a retrospective analysis, the clinical investigators of the trials discussed above found that subjects who responded to multiple peptides of the IMA901 vaccine were significantly (p = 0.019) more likely to experience disease control (stable disease, partial response) than subjects who responded only to one peptide or had no response. 6 of 8 subjects (75%) who responded to multiple peptides experienced clinical benefit in the trial, in contrast to 14% and 33% of 0 and 1 peptide responders, respectively. The randomized phase II trial confirmed that immune responses to multiple TUMAPs were associated with a longer overall survival.

Since the presence of PEPIs accurately predicted responders to TUMAPs, clinical responders to IMA901 are likely patients who can present ≥2 PEPIs from TUMAPs. This subpopulation is only 27% of HLA-A*02 selected patients, and according to the clinical trial result, 75% of this subpopulation is expected to experience clinical benefit. The same clinical results suggest that 100% of patients would experience clinical benefit if patient selection is based on ≥3 PEPIs from TUMAPs, albeit this population would represent only 3% of the HLA-A*02 selected patient population. These results suggest that the disease control rate (stable disease or partial response) is between 3% and 27% in the patient population which was investigated in the IMA901 clinical trials. In the absence of complete response, only a portion of these patients can experience survival benefit.

These findings explain the absence of improved survival in the Phase III IMA901 clinical trial. These results also demonstrated that HLA-A*02 enrichment of the study population was not sufficient to reach the primary overall survival endpoint in the Phase III IMA901 trial. As the IMA901 trial investigators noted, there is a need for the development of a companion diagnostic (CDx) to select likely responders to peptide vaccines. These findings also suggest that selection of patients with ≥2 TUMAP specific PEPIs may provide sufficient enrichment to demonstrate significant clinical benefit of IMA901.

Example 12 - *In silico* trial based on the identification of vaccine-derived multiple HLA binding epitopes predict reported experimental clinical response rates

Acorrelation between the ≥2 PEPI3+ Score of immunotherapy vaccines determined in the Model Population described in Example 8 and the reported Disease Control Rate (DCR, proportion of patients with complete responses and partial responses and stable disease) determined in clinical trials was determined.

Seventeen clinical trials, conducted with peptide- and DNA-based cancer immunotherapy vaccines that have published Disease Control Rates (DCRs) or objective response rate (ORR) were identified from peer reviewed scientific journals (Table 23). These trials involved 594 patients (5 ethnicities) and covered 29 tumor and viral antigens. DCRs were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), which is the current standard for clinical trials, in which clinical responses are based on changes in maximum cross-sectional dimensions[42, 43, 44]. In case there was no available DCR data, objective response rate (ORR) data was used, which is also defined according to the RECIST guidelines.

Table 24 compares the ≥2 PEPI3+ Score for each vaccine in the Model Population and the published DCR or ORR. A correlation between the predicted and measured DCR was observed providing further evidence that not only the immunogenicity but also the potency of cancer vaccines depends on the multiple HLA sequences of individuals (R2 = 0.76) (FIG. 9).

Table 23.Clinical trials selected for Disease Control Rate (DCR) prediction.

Immuno-therapy	Antigen	Sponsor	Disease	Pop. (n)	Study pop./ Ethnicity	HLA restriction	Adm. form	Dose (mg)	Dosing schedule	Assessment time (weeks)	Ref.
IMA901 phase I	9 TAAs	Immatics	Renal cell cancer	28	CEU	A02	i.d.	0.4	8x in 10 wks	12	19
IMA901 phase II	9 TAAs	Immatics	Renal cell cancer	68	CEU	A02	i.d	0.4	7x in 5 wks then 10x 3 wks	24	19
Ipilimumab	NY-ESO-1	MSKCC	Melanoma	19	US	no	i.v.	0.3 3 10	4 x every 3 wks	24	5
HPV-SLP*	HPV-16 E6, E7	Leiden University	VIN	20	CEU	no	s.c.	0.3	3 x every 3 wks	12	9
HPV-SLP*		Leiden University	HPV-related cervical cancer	5	CEU	no	s.c.	0.3	3 x every 3 wks	12 (OR)	10
gp100 - 2 peptides*	gp100	BMS	Melanoma	136	US	A*0201	s.c.	1	4 x every 3 wks	12	28
Immucin	Muc-1	VaxilBio	Myeloma	15	Israeli	no	s.c.	0.1	6 x every 2 wks	12**	29
StimuVax	Muc-1	Merck	NSCLC	80	Canadian	no	s.c.	1	8x wkly then every 6 wks	12	13, 30
VGX-3100	HPV-16&18	Inovio	HPV-related cervical cancer	125	US	no	i.m.	6	0, 4, 12 wks	36	31
TSPP peptide vaccine	Thymidylate synthase	Siena University	CRC, NSCLC, Gallbladder carc., Breast-, Gastric cancer	21	CEU	no	s.c.	0.1 0.2 0.3	3 x 3 wks	12	32
KIF20A-66 peptide vaccine*	KIF20A	Chiba Tokushukai Hospital	Metastatic pancreatic cancer	29	Japanese	A*2402	s.c.	1 3	2 cycles 1, 8, 15, 22 days then every 2 wks	12 (OR)	33
Peptide vaccine*	3 TAAs	Kumamoto University	HNSCC	37	Japanese	A*2402	s.c.	1	8 x wkly then every 4 wks	12	34
7-peptide cocktail vaccine*	7 TAAs	Kinki University	Metastatic colorectal cancer	30	Japanese	A*2402	s.c.	1	Cycles: 5 x wkly then 1 wk rest	10 (OR)	35
GVX301*	hTERT	University Genoa	Prostate and renal cancer	14	Japanese	A02	i.d.	0.5	1, 3, 5, 7, 14, 21, 35, 63 days	12	25
MAGE-A3 Trojan*	MAGE-A3	Abramson Cancer Center	Multiple myeloma	26	US	no	s.c.	0.3	14, 42, 90, 120, 150 days	24	36
PepCan	HPV-16 E6	University of Arkansas	CIN2/3	23	US	no	i.m.	0.05 0.1 0.25 0.5	4 x 3 wks	24	37
Melanoma peptide vaccine*	Tyrosinase, gp100	University of Virginia	Melanoma	26	US	A1, A2 or A3	s.c.	0.1	6 cycles: 0, 7, 14, 28, 35, 42 days	6	27

*Montanide ISA51 VG as adjuvant

**Disease response was assessed according to the International Myeloma Working Group response criteria[45]

Table 24. The Disease Control Rates (DCRs) and MultiPEPI Scores (predicted DCR) in 17 clinical trials.

Immunotherapy	DCR	MultiPEPI Score (Predicted DCR)	Overall Percentage of Agreement
IMA901 phase I	43%	27%	*61%*
IMA901 phase II	22%	27%	*81%*
Ipilimumab	60%	65%	*92%*
HPV-SLP	60%	70%	*86%*
HPV-SLP	62%	70%	*89%*
gp100 - 2 peptides	15%	11%	*73%*
Immucin	73%	59%	*81%*
StimuVax	0%	0%	*100%*
VGX-3100	50%	56%	*89%*
TSPP peptide vaccine	48%	31%	*65%*
KIF20A-66 peptide vaccine	26%	7%	*27%*
Peptide vaccine	27%	10%	*37%*
7-peptide cocktail vaccine	10%	9%	*90%*
GVX301	29%	7%	*24%*
MAGE-A3 Trojan	35%	10%	*29%*
PepCan	52%	26%	*50%*
Melanoma peptide vaccine	12%	6%	*50%*

Example 13 In silico trials based on the identification of multiple HLA binding epitopes predict the reported cellular immune response rates to a vaccine targeting a mutational antigen

The epidermal growth factor receptor variant III (EGFRvIII) is a tumor-specific mutation broadly expressed in glioblastoma multiforme (GBM) and other neoplasms. The mutation comprises an in-frame deletion of 801 bp from the extracellular domain of the EGFR that splits a codon and yields a novel glycine at the fusion junction.[1, 2] This mutation encodes a constitutively active tyrosine kinase that increases tumor formation and tumor cell migration and enhances resistance against radiation and chemotherapy.[3, 4, 5, 6, 7, 8, 9] This insertion results in a tumor-specific epitope which is not found in normal adult tissues making EGFRvIII a suitable target candidate for antitumor immunotherapy.[10] Rindopepimut is a 13-amino-acid peptide vaccine

(LEEKKGNYVVTDHC) spanning the EGFRvIII mutation with an additional C-terminal cysteine residue.[11]

In a phase II clinical study, the peptide conjugated to keyhole limpet hemocyanin (KLH) was administered to newly diagnosed EGFRvIII-expressing GBM patients. The first three vaccinations were given biweekly, starting 4 weeks after the completion of radiation. Subsequent vaccines were given monthly until radiographic evidence of tumor progression or death. All vaccines were given intradermally in the inguinal region. Immunologic evaluation showed only 3 out of 18 patients developing cellular immune response assessed by DTH reaction test.

An in silico trial with the Model Population of 433 subjects with Rindopepimut sequence was conducted. 4 out of 433 subjects had PEPI3+, confirming the low immunogenicity found in the phase II study (Table 25).

Table 25. Results of clinical trial and *in silico* study

	Responders	Response rate
Clinical trial (Phase II)	3/18	16.6%
In silico study (PEPI3+ Test)	4/433	1%

An HLA map of the Rindopepimut on the HLA alleles of the subjects in the Model Population (Fig. 10) illustrates that very few HLA-A and HLA-C alleles can bind the vaccine epitopes which explains the lack of PEPI3+ in the in silico cohort.

In a recent phase III clinical study the ineffectiveness was further demonstrated when 745 patients were enrolled and randomly assigned to Rindopepimut and temozolomide (n=371) or control and temozolomide (n=374) arms.[12] The trial was terminated for ineffectiveness after the interim analysis. The analysis showed no significant difference in overall survival: median overall survival was 20.1 months (95% CI 18.5–22.1) in the Rindopepimut group versus 20.0 months (18.1–21.9) in the control group (HR 1.01, 95% CI 0.79–1.30; p=0.93).

References for Example 13

1 Bigner et al. Characterization of the epidermal growth factor receptor in human glioma cell lines and xenografts. Cancer Res 1990;50: 8017–22.

2 Libermann et al. Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumours of glial origin. Nature 1985;313: 144–7.

3 Chu et al. Receptor dimerization is not a factor in the signalling activity of a transforming variant epidermal growth factor receptor (EGFRvIII). Biochem J 1997; 324: 855–61.

4 Batra et al. Epidermal growth factor ligand-independent, unregulated, cell-transforming potential of a naturally occurring human mutant EGFRvIII gene. Cell Growth Differ 1995;6: 1251–9.

5 Nishikawa et al. A mutant epidermal growth factor receptor common in human glioma confers enhanced tumorigenicity. PNAS 1994; 91: 7727–31.

6 Lammering et al. Inhibition of the type III epidermal growth factor receptor variant mutant receptor by dominant-negative EGFR-CD533 enhances malignant glioma cell radiosensitivity. Clin Cancer Res 2004; 10: 6732–43.

7 Nagane et al. A common mutant epidermal growth factor receptor confers enhanced tumorigenicity on human glioblastoma cells by increasing proliferation and reducing apoptosis. Cancer Res 1996; 56: 5079–86.

8 Lammering et al. Radiation-induced activation of a common variant of EGFR confers enhanced radioresistance. Radiother Oncol 2004; 72: 267–73.

9 Montgomery et al. Expression of oncogenic epidermal growth factor receptor family kinases induces paclitaxel resistance and alters β-tubulin isotype expression. J Biol Chem 2000; 275: 17358–63.

10 Humphrey et al. Anti-synthetic peptide antibody reacting at the fusion junction of deletion-mutant epidermal growth factor receptors in human glioblastoma. PNAS 1990; 87: 4207–11.

11 Sampson et al. Immunologic Escape After Prolonged Progression-Free Survival With Epidermal Growth Factor Receptor Variant III Peptide Vaccination in Patients With Newly Diagnosed Glioblastoma. J Clin Oncol 28:4722-4729.

12 Weller at al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol 2017; 18(10): 1373-1385.

Example 14. Multiple HLA binding peptides of individuals can predict immune-toxicity

Thrombopoietin (TPO) is a highly immunogenic protein drug causing toxicity in many patients. EpiVax/Genentech used State of Art technology to identify class II HLA restricted epitopes and found that the most immunogenic region of the TPO is located in the C-terminal end of TPO (US20040209324 A1).

According to the present disclosure we defined the multiple class II HLA binding epitopes (PEPI3+s) from TPO in 400 HLA class II genotyped US subjects were determined. Most of the PEPI3+ peptides of these individuals located within the N terminal region of the TPO between 1-165 amino acids. PEPI3+ were spopradically identified in some subjects also in the C terminal region. However, our results were different from the State of Art.

The published literature confirmed the disclosed results, demonstrating experimental proof for the immunotoxic region being located at the N-terminal end of TPO[40, 41]. Most individuals treated with TPO drug made anti-drug antibodies (ADA) ADA against this region of the drug. These antibodies not only abolished the therapeutic effect of the drug but also caused systemic adverse events, i.e. immune-toxicity, like antibody –dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity associated with thrombocytopenia, neutropenia and anemia. These data demonstrate that the identification of multiple HLA binding peptides of individuals predicts the immune-toxicity of TPO. Therefore, the discloure is useful to identify the toxic immunogenic region of drugs, to identify subjects who likely experience immune-toxicity from drugs, to identify regions of a polypeptide drug that may be targeted by ADAs, and to identify subjects who likely experience ADA.

Example 15 Personalised Immunotherapy Composition for Treatment of Ovarian Cancer

This example describes the treatment of an ovarian cancer patient with a personalised immunotherapy composition, wherein the composition was specifically designed for the patient based on her HLA genotype based on the disclosure described herein. This Example and Example 16 below provide clinical data to support the principals regarding binding of epitopes by multiple HLA of a subject to induce a cytotoxic T cell response on which the present disclosure is based.

The HLA class I and class II genotype of metastatic ovarian adenocarcinoma cancer patient XYZ was determined from a saliva sample.

To make a personalized pharmaceutical composition for patient XYZ thirteen peptides were selected, each of which met the following two criteria: (i) derived from an antigen that is expressed in ovarian cancers, as reported in peer reviewed scientific publications; and (ii) comprises a fragment that is a T cell epitope capable of binding to at least three HLA class I of patient XYZ (Table 26). In addition, each peptide is optimized to bind the maximum number of HLA class II of the patient.

Table 26: XYZ ovarian cancer patient's personalized vaccine

XYZ's vaccine	Target Antigen	Antigen Expression	20mer peptides	MAX HLA classI	MAX HLA classII
POC01_P1	AKAP4	89%	NSLQKQLQAVLQWIAASQFN	3	5
POC01_P2	BORIS	82%	SGDERSDEIVLTVSNSNVEE	4	2
POC01_P3	SPAG9	76%	VQKEDGRVQAFGWSLPQKYK	3	3
POC01_P4	OY-TES-1	75%	EVESTPMIMENIQELIRSAQ	3	4
POC01_P5	SP17	69%	AYFESLLEKREKTNFDPAEW	3	1
POC01_P6	WT1	63%	PSQASSGQARMFPNAPYLPS	4	1
POC01_P7	HIWI	63%	RRSIAGFVASINEGMTRWFS	3	4
POC01_P8	PRAME	60%	MQDIKMILKMVQLDSIEDLE	3	4
POC01_P9	AKAP-3	58%	ANSVVSDMMVSIMKTLKIQV	3	4
POC01_P10	MAGE-A4	37%	REALSNKVDELAHFLLRKYR	3	2
POC01_P11	MAGE-A9	37%	ETSYEKVINYLVMLNAREPI	3	4
POC01_P12a	MAGE-A10	52%	DVKEVDPTGHSFVLVTSLGL	3	4
POC01_P12b	BAGE	30%	SAQLLQARLMKEESPVVSWR	3	2

Eleven PEPI3 peptides in this immunotherapy composition can induce T cell responses in XYZ with 84% probability and the two PEPI4 peptides (POC01-P2 and POC01-P5) with 98% probability, according to the validation of the PEPI Test shown in Table 10. T cell responses target 13 antigens expressed in ovarian cancers. Expression of these cancer antigens in patient XYZ was not tested. Instead the probability of successful killing of cancer cells was determined based on the probability of antigen expression in the patient's cancer cells and the positive predictive value of the ≥1 PEPI3+ Test (AGP count). AGP count predicts the effectiveness of a vaccine in a subject: Number of vaccine antigens expressed in the patient's tumor (ovarian adenocarcinoma) with PEPI. The AGP count indicates the number of tumor antigens that vaccine recognizes and induces a T cell response against the patient's tumor (hit the target). The AGP count depends on the vaccine-antigen expression rate in the subject's tumor and the HLA genotype of the subject. The correct value must be between 0 (no PEPI presented by expressed antigen) and maximum number of antigens (all antigens are expressed and present a PEPI).

The probability that patient XYZ will express one or more of the 12 antigens is shown in Fig. 11. AGP95 = 5, AGP50 = 7.9, mAGP = 100%, AP = 13.

A pharmaceutical composition for patient XYZ may be comprised of at least 2 from the 13 peptides (Table 26), because the presence in a vaccine or immunotherapy composition of at least two polypeptide fragments (epitopes) that can bind to at least three HLA of an individual (≥2 PEPI3+) was determined to be predictive for a clinical response. The peptides are synthetized, solved in a pharmaceutically acceptable solvent and mixed with an adjuvant prior to injection. It is desirable for the patient to receive personalized immunotherapy with at least two peptide vaccines, but preferable more to increase the probability of killing cancer cells and decrease the chance of relapse.

For treatment of patient XYZ the 12 peptides were formulated as 4 x 3/4 peptide (POC01/1, POC01/2, POC01/3, POC01/4). One treatment cycle is defined as administration of all 13 peptides within 30 days.

Patient history:

Diagnosis: Metastatic ovarian adenocarcinoma

Age: 51

Family anamnesis: colon and ovary cancer (mother) breast cancer (grandmother)

Tumor pathology:

BRCA1-185delAG, BRAF-D594Y, MAP2K1-P293S, NOTCH1-S2450N

- 2011: first diagnosis of ovarian adenocarcinoma; Wertheim operation and chemotherapy; lymph node removal
- 2015: metastasis in pericardial adipose tissue, excised
- 2016: hepatic metastases
- 2017: retroperitoneal and mesenteric lymph nodes have progressed; incipient peritoneal carcinosis with small accompanying ascites

Prior Therapy:

- 2012: Paclitaxel-carboplatin (6x)
- 2014: Caelyx-carboplatin (1x)
- 2016-2017 (9 months): Lymparza (Olaparib) 2x400 mg/day, oral
- 2017: Hycamtin inf. 5x2,5 mg (3x one seria/month)

PIT vaccine treatment began on 21 April 2017.

Table 27 Patient XYZ peptide treatment schedule

Lot #		Vaccinations			
		1st cycle	2nd cycle	3rd cycle	4th cycle
POC01/1	N1727	21.04.2017	16.06.2017	30.08.2017	19.10.2017
POC01/2	N1728	28.04.2017	31.05.2017		
POC01/3	N1732		16.06.2017	02.08.2017	20.09.2017
POC01/4	N1736	15.05.2017	06.07.2017		

Patient' tumor MRI findings (Baseline April 15, 2016)

- Disease was confined primarily to liver and lymph nodes. The use of MRI limits detection of lung (pulmonary) metastasis
- May 2016 – Jan 2017: Olaparib treatment

- Dec/25/2016 (before PIT vaccine treatment) There was dramatic reduction in tumor burden with confirmation of response obtained at FU2
- Jan - Mar 2017 – TOPO protocol (topoisomerase)
- April/6/2017 FU3 demonstrated regrowth of existing lesions and appearance of new lesions leading to disease progression
- **April 21 2017 START PIT**
- Jul/21/17 (after the 2nd Cycle of PIT) FU4 demonstrated continued growth in lesions and general enlargement of pancreas and abnormal para pancreatic signal along with increased ascites
- Jul/26/17 – CBP+Gem+Avastin
- Sep/20/17 (after 3 Cycles of PIT) FU5 demonstrated reversal of lesion growth and improved pancreatic/parapancreatic signal. The findings suggest pseudo progression
- Nov 28/17 (after 4 Cycles of PIT) FU6 demonstrated best response with resolution of non target lesions

MRI data for patient XYZ is shown in Table 28 and Figure 12.

Table 28. Summary Table of Lesions Responses

Lesion/ Time Point	Baseline (%Δ from BL)	FU1 (%Δ from BL)	FU2 (%Δ from BL)	FU3 (%Δ from BL)	FU4 (%Δ from BL)	FU5 (%Δ from BL)	FU6 (%Δ from BL)	Best Response Cycle	PD Time Point
TL1	NA	-56.1	-44.4	-44.8	+109.3	-47.8	-67.3	**FU6**	**FU4**
TL2	NA	-100.0	-100.0	-47.1	-13.1	-100.0	-100.0	**FU1**	**FU3**
TL3	NA	-59.4	-62.3	-62.0	-30.9	-66.7	-75.9	**FU6**	**FU4**
TL4	NA	-65.8	-100.0	-100.0	-100.0	-100.0	-100.0	**FU2**	**NA**
SUM	NA	-66.3	-76.0	-68.9	-23.5	-78.2	-85.2	**FU6**	**FU4**

Example 16 Design of Personalised Immunotherapy Composition for Treatment of Breast Cancer

The HLA class I and class II genotype of metastatic breast cancer patient ABC was determined from a saliva sample. To make a personalized pharmaceutical composition for patient ABC twelve peptides were selected, each of which met the following two criteria: (i)

derived from an antigen that is expressed in breast cancers, as reported in peer reviewed scientific publications; and (ii) comprises a fragment that is a T cell epitope capable of binding to at least three HLA class I of patient ABC (Table 29). In addition, each peptide is optimized to bind the maximum number of HLA class II of the patient. The twelve peptides target twelve breast cancer antigens. The probability that patient ABC will express one or more of the 12 antigens is shown in Figure 13.

Table 29. 12 peptides for ABC breast cancer patient

BRC09 vaccine peptides	Target Antigen	Antigen Expression	20mer peptide	MAXHLA Class I	MAXHLA Class II
PBRC01_cP1	FSIP1	49%	ISDTKDYFMSKTLGIGRLKR	3	6
PBRC01_cP2	SPAG9	88%	FDRNTESLFEELSSAGSGLI	3	2
PBRC01_cP3	AKAP4	85%	SQKMDMSNIVLMLIQKLLNE	3	6
PBRC01_cP4	BORIS	71%	SAVFHERYALIQHQKTHKNE	3	6
PBRC01_cP5	MAGE-A11	59%	DVKEVDPTSHSYVLVTSLNL	3	4
PBRC01_cP6	NY-SAR-35	49%	ENAHGQSLEEDSALEALLNF	3	2
PBRC01_cP7	HOM-TES-85	47%	MASFRKLTLSEKVPPNHPSR	3	5
PBRC01_cP8	NY-BR-1	47%	KRASQYSGQLKVLIAENTML	3	6
PBRC01_cP9	MAGE-A9	44%	VDPAQLEFMFQEALKLKVAE	3	8
PBRC01_cP10	SCP-1	38%	EYEREETRQVYMDLNNNIEK	3	3
PBRC01_cP11	MAGE-A1	37%	PEIFGKASESLQLVFGIDVK	3	3
PBRC01_cP12	MAGE-C2	21%	DSESSFTYTLDEKVAELVEF	4	2

Predicted efficacy: AGP95=4; 95% likelihood that the PIT Vaccine induces CTL responses against 4 CTAs expressed in the breast cancer cells of BRC09. Additional efficacy parameters: AGP50 = 6.3, mAGP = 100%, AP = 12.

Detected efficacy after the 1st vaccination with all 12 peptides: 83% reduction of tumor metabolic activity (PET CT data).

For treatment of patient ABC the 12 peptides were formulated as 4 x 3 peptide (PBR01/1, PBR01/2, PBR01/3, PBR01/4). One treatment cycle is defined as administration of all 12 different peptide vaccines within 30 days.

Patient history

Diagnosis: bilateral metastatic breast carcinoma: Right breast is ER positive, PR negative, Her2 negative; Left Breast is ER, PR and Her2 negative.

First diagnosis: 2013 (4 years before PIT vaccine treatment)

2016: extensive metastatic disease with nodal involvement both above and below the diaphragm. Multiple liver and pulmonar metastases.

2016-2017 treatment: Etrozole, Ibrance (Palbociclib) and Zoladex

Results

Mar 7, 2017: Prior PIT Vaccine treatment

Hepatic multi-metastatic disease with truly extrinsic compression of the origin of the choledochal duct and massive dilatation of the entire intrahepatic biliary tract. Celiac, hepatic hilar and retroperitoneal adenopathy

May 26 2017: After 1 cycle of PIT

Detected efficacy: 83% reduction of tumor metabolic activity (PET CT) liver, lung lymphnodes and other metastases. Detected safety: Skin reactions

Local inflammation at the site of the injections within 48 hours following vaccine administrations

Follow up:

BRC-09 was treated with 5 cycles of PIT vaccine. She was feeling very well and she refused a PET CT examination in Sept 2017. In November she had symptoms, PET CT scan showed progressive disease, but she refused all treatments. In addition, her oncologist found out that she did not take Palbocyclib since spring/summer. Patient ABC passed away in Jan 2018.

The combination of pablocyclib and the personalised vaccine was likely to have been responsible for the remarkable early response observed following administration of the vaccine. Palbocyclib has been shown to improve the activity of immunotherapies by increases CTA presentation by HLAs and decreasing the proliferation of Tregs: (Goel et al. Nature. 2017:471-475). The PIT vaccine may be used as add-on to the state-of-art therapy to obtain maximal efficacy.

Example 17. Breast cancer vaccine design for large population and composition

We used the PEPI3+ Test described above to design peptides for use in breast cancer vaccines that are effective in a large percentage of patients, taking into account the heterogeneities of both tumour antigens and patients' HLAs.

Breast cancer CTAs were identified and ranked based on the overall expression frequencies of antigens found in breast cancer tumor samples as reported in peer reviewed publications (Chen et al. Multiple Cancer/Testis Antigens Are Preferentially Expressed in Hormone-Receptor Negative and High-Grade Breast Cancers. Plos One 2011; 6(3): e17876.; Kanojia et al. Sperm-Associated Antigen 9, a Novel Biomarker for Early Detection of Breast Cancer. Cancer Epidemiol Biomarkers Prev 2009; 18(2):630 –639.; Saini et al. A Novel Cancer Testis Antigen, A-Kinase Anchor Protein 4 (AKAP4) Is a Potential Biomarker for Breast Cancer. Plos One 2013; 8(2): e57095).

For select CTAs we used the PEPI3+ Test and the Model Population described in Example 8 to identify the 9 mer epitopes (PEPI3+s) that are most frequently presented by at least 3HLAs of the individuals in the Model Population. We refer to these epitopes herein as "bestEPIs". An illustrative example of the "PEPI3+ hotspot" analysis and bestEPI identification is shown in FIG. 14 for the PRAME antigen.

We multiplied the reported expression frequency for each CTA (N%) by the frequency of the PEPI3+ hotspots in the Model Population (B%) to identify the T cell epitopes (9 mers) that will induce an immune response against breast cancer antigens in the highest proportion of individuals (Table 30). We then selected 15 mers encompassing each of the selected 9 mers (Table 30). The 15 mers were selected to bind to most HLA class II alleles of most subjects, using the process described in Example 22 below. These 15 mers can induce both CTL and T helper responses in the highest proportion of subjects.

Table 30 BestEPI list for selecting breast cancer peptide vaccine composition. Ntotal: number of samples analyzed for the expression of the certain antigen; N+: number of individuals expressing the certain antigen; N%: expression frequency of the certain antigen; B%: bestEPI frequency, ie.

the percentage of individuals having the bestEPI within the model population; N%*B%: expression frequency multiplied by the bestEPI frequency.

Antigen Information					BestEPIs			
Gene	length	Ntotal	N+	N%	SEQ	Position	B%	N%*B%
AKAP-4	854	91	77	85%	YLMNRPQNL	167	52%	44%
AKAP-4	854	91	77	85%	MMAYSDTTM	1	49%	41%
BORIS	663	58	41	71%	FTSSRMSSF	264	57%	40%
AKAP-4	854	91	77	85%	YALGFQHAL	121	46%	39%
SPAG9	1321	100	88	88%	KMSSLLPTM	964	43%	38%
SPAG9	1321	100	88	88%	FTVCNSHVL	785	36%	31%
BORIS	663	58	41	71%	MAFVTSGEL	320	44%	31%
PRAME	509	100	55	55%	YLHARLREL	462	52%	28%
SPAG9	1321	100	88	88%	VMSERVSGL	19	28%	25%
BORIS	663	58	41	71%	FTQSGTMKI	407	35%	25%
NY-SAR-35	255	29	14	48%	FSSSGTTSF	163	45%	22%
MAGE-A9	315	142	63	44%	FMFQEALKL	102	49%	22%
NY-SAR-35	255	29	14	48%	FVLANGHIL	97	42%	21%
PRAME	509	100	55	55%	KAMVQAWPF	70	37%	20%
NY-BR-1	1341	131	61	47%	YSCDSRSLF	424	39%	18%
Survivin	142	167	118	71%	RAIEQLAAM	133	26%	18%
MAGE-A11	429	135	79	59%	AMDAIFGSL	184	23%	14%
HOM-TES-85	313	100	47	47%	MASFRKLTL	1	29%	13%
MAGE-A9	315	142	63	44%	SSISVYYTL	67	30%	13%
NY-BR-1	1341	131	61	47%	SAFEPATEM	584	27%	12%

Then we designed 31 30 mer peptides. Each consists of two optimized 15 mer fragments, generally from different frequent CTAs, arranged end to end, each fragment comprising one of the 9 mers (BestEPIs) from Table 30. Nine of these 30 mer peptides were selected for a panel of peptides, referred to as PolyPEPI915 (Table 31). Expression frequencies for the 10 CTAs targeted by PolyPEPI915, singly and in combination, are shown in FIG. 15.

Table 31 – Selected Breast Cancer Vaccine peptides for PolyPEPI915 panel/composition

TREOSID	Source Antigen	Peptide (30mer)	HLAI* (CD8)	HLAII** (CD4)
BCV900-4-1	SPAG9/AKAP4	GNILDSFTVCNSHVLLQKYALGFQHALSPS	53%	75%
BCV900-4-2	BORIS/NY-SAR-35	NMAFVTSGELVRHRRFSSSGTTSFKCFAPF	65%	46%
BCV900-3-3	NY-BR-1/SURVIVIN	YSCDSRSLFESSAKITAKKVRRAIEQLAAM	55%	11%
BCV900-3-4	AKAP-4/BORIS	MMAYSDTTMMSDDIDHTRFTQSGTMKIHIL	72%	45%

BCV900-4-5	SPAG9/BORIS	AQKMSSLLPTMWLGAMFTSSRMSSFNRHMK	72%	50%
BCV900-5-6	HomTes85/MageA11	MASFRKLTLSEKVPPSPTAMDAIFGSLSDE	45%	16%
BCV900-5-7	AKAP4/PRAME	DQVNIDYLMNRPQNLRHSQTLKAMVQAWPF	64%	33%
BCV900-5-8	NYSAR/SPAG9	CSGSSYFVLANGHILSGAVMSERVSGLAGS	46%	48%
BCV900-3-9	PRAME/MAGE-A9	LERLAYLHARLRELLQLEFMFQEALKLKVA	73%	100%
		PolyPEPI915 (9 peptide together)	96%	100%

* Percentage of individuals having CD8+ T cell specific PEPI3+ within the Model Population (n=433).
**Percentage of individuals having CD4+ T cell specific PEPI4+ within the Model Population (n=433).

Characterization of PolyPEPI915

Tumor heterogeneity can be addressed by including peptide sequences that target multiple CTAs in a vaccine or immunotherapy regime. The PolyPEPI915 composition targets 10 different CTAs. Based on the antigen expression rates for these 10 CTAs, we modelled the predicted average number of expressed antigens (AG50) and the minimum number of expressed antigens with 95% likelihood (AG95) in the cancer cells. 95% of individuals expressed minimum 4 of the 10 target antigens (AG95=4) as shown by the antigen expression curve in FIG. 16.

The AG values described above characterize a vaccine independently from the target patient population. They can be used to predict the likelihood that a specific cancer (e.g. breast cancer) expresses antigens targeted by a specific vaccine or immunotherapy composition. AG values are based on known tumor heterogeneity, but do not take HLA heterogeneity into account.

HLA heterogeneity of a certain population can be characterised from the viewpoint of an immunotherapy or vaccine composition by the number of antigens representing PEPI3+. These are the vaccine-specific CTA antigens for which ≥1 PEPI3+ is predicted, referred to herein as the "AP". The average number of antigens with PEPI3+ (AP50) shows how the vaccine can induce immune response against the antigens targeted by the composition (breast cancer vaccine specific immune response). The PolyPEPI915 composition can induce immune response against an average of 5.3 vaccine antigens (AP50=5.30) and 95% of the Model Population can induce immune response against at least one vaccine antigen (AP95=1)(FIG. 17).

Vaccines can be further characterized by AGP values that refers to antigens with PEPIs". This parameter is the combination of the previous two parameters: (1) AG is depending on the antigen expression frequencies in the specific tumor type but not on the HLA genotype of

individuals in the population, and (2) AP is depending on the HLA genotype of individuals in a population without taking account the expression frequencies of the antigen. The AGP is depending on both, the expression frequencies of vaccine antigens in the disease and the HLA genotype of individuals in a population.

Combining the data of AG of breast cancer and AP in the Model Population we determined the AGP value of PolyPEPI915 that represents the probability distribution of vaccine antigens that are induce immune responses against antigens expressed in breast tumors. For PolyPEPI915, the AGP50 value in the Model Population is 3.37. The AGP92=1, means that 92% of the subjects in the Model Population induce immune responses against at least one expressed vaccine antigen (FIG. 18).

Example 18 – Likely responder patient selection using companion diagnostic tests for vaccines

The likelihood that a specific patient will have an immune response or a clinical response to treatment with one or more cancer vaccine peptides, for example as described above, can be determined based on (i) the identification of PEPI3+ within the vaccine peptide(s) (9 mer epitopes capable of binding at least three HLA of the patient); and/or (ii) a determination of target antigen expression in cancer cells of the patient, for example as measured in a tumour biopsy. In some cases both parameters are ideally determined and the optimal combination of vaccine peptides is selected for use in treatment of the patient. However, PEPI3+ analysis alone may be used if a determination of the expressed tumour antigens, for example by biopsy, is not possible, not advised, or unreliable due to biopsy error (i.e. biopsy tissue samples taken from a small portion of the tumor or metastasised tumors do not represent the complete repertoire of CTAs expressed in the patient).

Example 19 - Comparison of PolyPEPI915 with competing breast cancer vaccines

We used the *in silico* clinical trial model described in above to predict the immune response rates of competing breast cancer vaccines that have been investigated in clinical trials (Table 32). The immune response rate of these products were between 3% and 91%.

The single peptide vaccines were immunogenic in 3% - 23% of individuals. In comparison, the 30 mer peptides described in Example 18 above (Table 29) were each immunogenic in from 44% to 73% of individuals in the same cohorts. This result represents substantial improvement in immunogenicity of each peptide in PolyPEPI915.

Competing combination peptide products immune response rates were between 10 - 62%. The invented PolyPEPI915 combination product were 96% in the Model Population and 93% in a breast cancer patient population, representing improvement in immunogenicity.

Table 32. Predicted immune response rates of competing breast cancer vaccines

Breast Cancer Vaccines	Sponsors	Target antigens	Predicted immune response rates*	
			433 normal donors (Model Population)	90 patients with breast cancer
DPX0907 Multipeptide	ImmunoVaccine Tech.	7	58%	62%
Multipeptide vaccine	University of Virginia	5	22%	31%
Ad-sig-hMUC-1/ecdCD40L	Singapore CRI	1	91%	80%
NY-ESO-1 IDC-G305	Immune Design Corp.	1	84%	84%
6 HER2 peptide pulsed DC	University Pennsylvania	1	29%	36%
HER-2 B Cell peptide	Ohio State University	1	18%	23%

HER-2/neu ID protein	University Washington	1	10%	11%
NeuVax peptide	Galena Biopharma	1	6%	3%
StimuVax®(L-BLP25) peptide	EMD Serono	1	6%	8%
PolyPEPI915	Treos Bio	10	96%	93%

*Proportion of subjects with ≧1 PEPI3+

Another improvement of using the PolyPEPI915 vaccine is the lower chance of tumor escape. Each 30 mer peptide in PolyPEPI915 targets 2 tumor antigens. CTLs against more tumor antigens are more effective against heterologous tumor cells that CTLs against a single tumor antigen.

Another improvement is that PolyPEPI915 vaccine is that individuals who likely respond to vaccination can be identified based on their HLA genotypes (sequence) and optionally antigen expression in their tumor using the methods described here. Pharmaceutical compositions with PolyPEPI vaccines will not be administered to individuals whose HLA cannot present any PEPI3 from the vaccines. During clinical trials correlation will be made between the mAGP or number of AGP in the PolyPEPI915 regimen and the duration of individual's responses. A vaccine combination with > 1 AGP is most likely required to destroy heterologous tumor cells.

Example 20 Colorectal cancer vaccine design and composition

We show another example for colorectal vaccine composition using the same design method demonstrated above. We used the PEPI3+ Test described above to design peptides for use in colorectal cancer vaccines that are effective in a large percentage of patients, taking into account the heterogeneities of both tumour antigens and patient HLAs.

Colorectal cancer CTAs were identified and ranked based on the overall expression frequencies of antigens found in colorectal cancer tumor samples as reported in peer reviewed publications (FIG. 19) (Choi J, Chang H. The expression of MAGE and SSX, and correlation of COX2, VEGF, and survivin in colorectal cancer. Anticancer Res 2012. 32(2):559-564.;

Goossens-Beumer IJ, Zeestraten EC, Benard A, Christen T, Reimers MS, Keijzer R, Sier CF, Liefers GJ, Morreau H, Putter H, Vahrmeijer AL, van de Velde CJ, Kuppen PJ. Clinical prognostic value of combined analysis of Aldh1, Survivin, and EpCAM expression in colorectal cancer. Br J Cancer 2014. 110(12):2935-2944.; Li M, Yuan YH, Han Y, Liu YX, Yan L, Wang Y, Gu J. Expression profile of cancer-testis genes in 121 human colorectal cancer tissue and adjacent normal tissue. Clinical Cancer Res 2005. 11(5):1809–1814).

For the selection of the most frequently expressed colorectal cancer CTAs we used the PEPI3+ Test and the Model Population described in Example 8 to identify the "bestEPIs".

We multiplied the reported expression frequency for each CTA (N%)by the frequency of the PEPI3+ hotspots in the Model Population (B%) to identify the T cell epitopes (9 mers) that will induce an immune response against colorectal cancer antigens in the highest proportion of individuals (Table 33). We then selected 15 mers encompassing each of the selected 9 mers (Table 33). The 15 mers were selected to bind to most HLA class II alleles of most subjects, using the process described in Example 22 below. These 15 mers can induce both CTL and T helper responses in the highest proportion of subjects.

Table 33 BestEPI list for selecting colorectal cancer peptide vaccine composition. Ntotal: number of biopsy samples (tumor specific antigen expression in human colorectal cancer tissues) analyzed for the expression of the certain antigen; N+: number of individuals expressing the certain antigen; N%: expression frequency of the certain antigen; B%: bestEPI frequency, ie. the percentage of induviduals having the bestEPI within the model population; N%*B%: expression frequency multiplied by the bestEPI frequency.

Antigen Information					BestEPIs			
Gene	LEN	Ntotal	N+	N%	SEQ	POS	B%	N%*B%
TSP50	385	95	85	89%	FSYEQDPTL	106	51%	45.7%
EpCAM	314	309	273	88%	RTYWIIIEL	140	51%	45.1%
TSP50	385	95	85	89%	TTMETQFPV	85	36%	32.6%
Spag9	1321	78	58	74%	FSFVRITAL	1143	44%	32.6%
Spag9	1321	78	58	74%	KMSSLLPTM	964	43%	32.1%
CAGE1	777	47	35	74%	KMHSLLALM	616	42%	31.5%
FBXO39	442	57	22	39%	FMNPYNAVL	96	78%	30.1%

CAGE1	777	47	35	74%	KSMTMMPAL	760	37%	27.3%
EpCAM	314	309	273	88%	YVDEKAPEF	251	28%	24.7%
FBXO39	442	57	22	39%	KTMSTFHNL	218	58%	22.2%
Survivin	142	309	267	86%	RAIEQLAAM	133	26%	22.2%
Spag9	1321	78	58	74%	VMSERVSGL	19	28%	21.0%
TSP50	385	95	85	89%	YRAQRFWSW	192	20%	17.8%
FBXO39	442	57	22	39%	FFFERIMKY	287	46%	17.6%
Survivin	142	309	267	86%	STFKNWPFL	20	15%	13.0%
Mage-A8	318	80	35	44%	AIWEALSVM	223	20%	8.7%
Mage-A8	318	80	35	44%	KVAELVRFL	115	18%	7.7%
Mage-A6	314	250	69	28%	FVQENYLEY	250	27%	7.5%
Mage-A8	318	80	35	44%	RALAETSYV	279	16%	7.1%
Mage-A6	314	250	69	28%	YIFATCLGL	176	25%	6.9%

Then we designed 31 30 mer peptides. Each consist of two optimized 15 mer fragments, generally from different frequent CTAs, where the 15 mer fragments are arranged end to end, each fragment comprising one of the 9 mers (BestEPIs) described above. Nine of these 30 mer peptides were selected for a panel of peptide vaccines, referred to as PolyPEPI1015 (Table 34). Expression frequencies for the 8 CTAs targeted by PolyPEPI1015, singly and in combination, are shown in FIG. 19.

Table 34 – Selected Colorectal Cancer Vaccine peptides for PolyPEPI1015 composition

TREOSID	Source Antigen	Peptide (30mer)	HLAI* (CD8)	HLAII** (CD4)
CCV1000-5-1	TSP50	PSTTMETQFPVSEGKSRYRAQRFWSWVGQA	53%	53%
CCV1000-2-2	EpCAM/Survivin	VRTYWIIIELKHKARTAKKVRRAIEQLAAM	57%	98%
CCV1000-5-3	EpCAM /Mage-A8	YVDEKAPEFSMQGLKDEKVAELVRFLLRKY	43%	72%
CCV1000-5-4	TSP50/Spag9	RSCGFSYEQDPTLRDGTGKLGFSFVRITAL	67%	82%
CCV1000-5-5	Mage-A8/Mage-A6	SRAPEEAIWEALSVMQYFVQENYLEYRQVP	45%	76%
CCV1000-2-6	CAGE1/Survivin	LASKMHSLLALMVGLKDHRISTFKNWPFLE	58%	95%
CCV1000-5-7	CAGE1/Spag9	PKSMTMMPALFKENRSGAVMSERVSGLAGS	57%	57%
CCV1000-2-8	FBXO39	KFMNPYNAVLTKKFQKVNFFFERIMKYERL	90%	98%
CCV1000-2-9	Spag9/FBXO39	AQKMSSLLPTMWLGAFKKTMSTFHNLVSLN	67%	66%
		PolyPEPI1015 (9 peptide together)	100%	99%

* Percentage of individuals having CD8+ T cell specific PEPI3+ within the Model Population (n=433).
**Percentage of individuals having CD4+ T cell specific PEPI4+ within the Model Population (n=433).

Characterization of PolyPEPI1015 colorectal cancer vaccine

Tumor heterogeneity: The PolyPEPI1015 composition targets 8 different CTAs (Fig 19). Based on the antigen expression rates for these 8 CTAs, AG50 = 5.22 and AG95 = 3 (FIG. 20). Patient heterogeneity: the AP50=4.73 and AP95 = 2 (AP95=2) (FIG. 21). Both tumor and patient heterogeneity: AGP50 = 3.16 and AGP95 = 1 (Model Population) (FIG. 22).

Example 21 - Comparison of colorectal cancer vaccine peptides with competing colorectal cancer vaccines

We used the *in silico* clinical trial model described above to determine T cell responder rate of state of art and currently developed CRC peptide vaccines and compared to that of polyPEPI1015 (Table 34). Our PEPI3+ test demonstrates that competing vaccines can induce immune responses against one tumor antigen in a fraction of subjects (2% - 77%). However, the multi-antigen (multi-PEPI) response determination for the 2 competitor multi-antigen vaccines resulted in no or 2% responders. *% of responders are the ratio of subjects from the Model population with 1≥PEPI3+ for HLAI (CD8+ T cell responses) in case of 1, or for 2, 3, 4 or 5 antigens of the vaccine compositions. Since multi-PEPI responses correlate with clinical responses induced by tumor vaccines, it is unlikely that any of the competing vaccines will demonstrate clinical benefit in 98% of patients. In contrast, we predicted multi-PEPI responses in 95% of subjects suggesting the likelihood for clinical benefit in the majority of patients.

Table 35 Predicted immune response rates of polyPEPI1015 and competing colorectal cancer vaccines

Colorectal Cancer Vaccines	**Sponsor**	**% of CD8+ T cell responders in 433 subjects***					
		Vaccine antigens (Ags)	% responders against multiple Ags				
			1 Ag	2 Ags	3 Ags	4 Ags	5 Ags
Stimuvax® (L-BLP25) Peptide Vaccine	Johannes Gutenberg University Mainz	1	6%	-	-	-	-

WT1 Multipeptide Vaccine	Shinshu University, Japan	1	79%	-	-	-	-
Multiepitope Peptide Cocktail Vaccine	Kinki University	7	5%	2%	0%	0%	0%
p53 Synthetic Long Peptide Vaccine	Leiden University Medical Center	1	77%	-	-	-	-
HER-2 B Cell Peptide Vaccine	Ohio State University Comprehensive Cancer Center	1	18%	-	-	-	-
NY-ESO-1 peptide pulsed dendritic cell vaccine	Jonsson ComprehensiveCancer Center	1	0%	-	-	-	-
OCV-C02	Otsuka Pharmaceutical Co., Ltd.	2	2%	0%	-	-	-
TroVax vaccine (OXB-301)	Oxford BioMedica	1	94%	-	-	-	-
ImMucin	Vaxil Bio Theapeutics	1	95%	-	-	-	-
PolyPEPI 1015	**Treos Bio**	**8**	100%	95%	87%	70%	54%

Example 22. Efficacy by design procedure exemplified for PolyPEPI1018 colorectal cancer vaccine

The PolyPEPI1018 Colorectal Cancer (CRC) Vaccine (PolyPEPI1018) composition is a peptide vaccine intended to be used as an add-on immunotherapy to standard-of-care CRC treatment options in patients identified as likely responders using a companion *in vitro* diagnostic test (CDx). Clinical trials are ongoing in the US and Italy to evaluate PolyPEPI1018 in metastatic colorectal cancer patients. The product contains 6 peptides (6 of the 30 mer peptides PolyPEPI1015 described in examples 18 to 20 mixed with the adjuvant Montanide. The 6 peptides were selected to induce T cell responses against 12 epitopes from 7 cancer testis antigens (CTAs) that are most frequently expressed in CRC. The 6 peptides were optimized to induce long lasting CRC specific T cell responses. Likely responder patients with T cell responses against multiple CTAs expressed in the tumor can be selected with a companion diagnostic (CDx). This example sets out the precision process used to design PolyPEPI1018. This process can be applied to design vaccines against other cancers and diseases.

A. Selection of Multiple Antigen Targets

The selection of tumor antigens is essential for the safety and efficacy of cancer vaccines. The feature of a good antigen is to have restricted expression in normal tissues so that autoimmunity is prevented. Several categories of antigen meet this requirement, including uniquely mutated antigens (e.g. p53), viral antigens (e.g. human papillomavirus antigens in cervical cancer), and differentiation antigens (e.g. CD20 in B-cell lymphoma).

The inventors selected multiple cancer testis antigens (CTAs) as target antigens since they are expressed in various types of tumor cells and testis cells, but not expressed in any other normal somatic tissues or cells. CTAs are desirable targets for vaccines for at least the following reasons:

- tumors of higher histological grade and later clinical stage often show higher frequency of CTA expression
- only a subpopulation of tumor cells express a certain CTA
- different cancer types are significantly different in their frequency of CTA expression
- tumors that are positive for a CTA often show simultaneous expression of more than one CTA
- None of the CTAs appear to be cell surface antigens, therefore these are unique targets for cancer vaccines (they are not suitable targets for antibody based immunotherapies)

To identify the target CTAs for PolyPEPI1018, the inventors built a CTA expression knowledgebase. This knowledgebase contains CTAs that are expressed in CRC ranked in order by expression rate. Correlation studies conducted by the inventors (see Example 11) suggest that vaccines which induce CTL responses against multiple antigens that are expressed in tumor cells can benefit patients. Therefore, seven CTAs with high expression rates in CRC were selected for inclusion in PolyPEPI1018 development. Details are set out in Table 36.

Table 36 Target CTAs in PolyPEPI1018 CRC vaccine

CTA Name	Expression Rate Characterization

TSP50	89.47%	*Testis-Specific Protease-Like Protein 50* is an oncogene which induces cell proliferation, cell invasion, and tumor growth. It is frequently expressed in gastric-, breast-, cervical- and colorectal cancer samples; and rarely expressed in normal human tissues, except in spermatocytes of testes.
EpCAM	88.35%	*Epithelial Cell Adhesion Molecule* is a tumor associated antigen, which is expressed in colon cancers and over-expressed in various human carcinomas. The high expression of EpCAM in cancer-initiating stem cells makes it a valuable target for cancer vaccines. EpCAM is also expressed in at low or negligible levels in normal epithelial cells, with the exception of squamous epithelium, hepatocytes and keratinocytes.
Survivin	87.28%	*Survivin (Baculoviral IAP repeat-containing protein 5)* is a multi-tasking protein that promotes cell proliferation and inhibits apoptosis. Though it is strongly expressed in fetal tissues and necessary for normal development, it is not expressed in most adult tissues. Survivin is expressed in various cancers including carcinomas. Normal tissues that express low level survivin include thymus, $CD34^+$ bone-marrow-derived stem cells, and basal colonic epithelium. Dramatic over-expression of survivin compared with normal tissues iis observed in tumors in the lung, breast, colon, stomach, esophagus, pancreas, bladder, uterus, ovaries, large-cell non-Hodgkin's lymphoma, leukemias, neuroblastoma, melanoma and non-melanoma skin cancers.
CAGE1	74.47%	*Cancer-associated gene 1 protein* is a typical CTA, which might play a role in cell proliferation and tumorigenesis. CAGE1 is highly expressed in colorectal cancer tissues and weakly expressed in adjacent normal colorectal mucosa. In addition, CAGE1 is expressed in melanoma, hepatoma, and breast tumors. No CAGE1 protein expression is detected in healthy human tissues, other than testes.
SPAG9	74.36%	*Sperm-associated antigen 9* is involved in c-Jun N-terminal kinase-signaling and functions as a scaffold protein, thus playing an important role in cell survival, proliferation, apoptosis and tumor development. SPAG9 expression was detected in epithelial ovarian cancer (90%), breast cancer (88%), cervical cancer (82%), renal cell cancer (88%) and colorectal cancer (74%) patients. None of the adjacent noncancerous tissues showed antigen expression. SPAG9 expression is restricted to testis.
FBXO39	38.60%	*FBXO39 (BCP-20)* is a testis specific protein and is an important part of the E3 ubiquitin ligase complex. It participates in ubiquitination and has a role in regulating the cell cycle, immune responses, signaling, and proteasomal degradation of proteins. FBXO39 is expressed in colon and breast cancers. FBXO39 expression has also been detected in ovary, placenta, and lung. FBXO39 expression is 100-fold higher in testis and 1,000-fold higher in colorectal cancers compared with normal tissue.
MAGEA8	43.75%	*Melanoma-associated antigen 8* function is not known, though it may play a role in embryonal development and tumor transformation or aspects of tumor progression. MAGE-A8 gene is expressed in CRC and hepatocellular carcinoma. MAGE-A8 expression in normal tissues is restricted to the testis and the placenta.

B. Precise Targeting is Achieved by PEPI3+ Biomarker Based Vaccine Design

As described above the PEPI3+ biomarker predicts a subject's vaccine induced T cell responses. The inventors developed and validated a test to accurately identify the PEPIs from antigen sequences and HLA genotypes (Examples 1, 2, 3). The PEPI Test algorithm was used to

identify the dominant PEPIs (besEPIs) from the 7 target CTAs to be included in PolyPEPI1018 CRC vaccine.

The dominant PEPIs identified with the process described here can induce CTL responses in the highest proportion of subjects:

i. Identification of all HLA class I binding PEPIs from the 7 CTA targets in each of the 433 subjects in the Model Population

ii. Identification of the dominant PEPIs (BestEPIs) that are PEPIs present in the largest subpopulation.

The 12 dominant PEPIs that are derived from the 7 CTAs in PolyPEPI1018 are presented in the following table. The PEPI % in Model Population indicates the proportion of 433 subjects with the indicated PEPI, i.e. the proportion of subjects where the indicated PEPI can induce CTL responses. There is very high variability (18% - 78%) in the dominant PEPIs to induce CTL responses despite the optimization steps used in the identification process.

Table 37 CRC specific HLA class I binding dominant PEPIs in PolyPEPI1018

Dominant PEPI3+ for each of the 7 CTAs in PolyPEPI1018 in CRC patients			
Peptides in PolyPEPI1018	**CRC Antigens**	**Dominant PEPI3+**	**PEPI3+% in Model Population**
CRC-P1	TSP50	TTMETQFPV	36%
		YRAQRFWSW	20%
CRC-P2	EpCAM	RTYWIIIEL	51%
	Survivin	RAIEQLAAM	26%
CRC-P3	EpCAM	YVDEKAPEF	28%
	MAGE-A8	KVAELVRFL	18%
CRC-P6	CAGE1	KMHSLLALM	42%
	Survivin	STFKNWPFL	15%
CRC-P7	CAGE1	KSMTMMPAL	37%
	SPAG9	VMSERVSGL	28%
CRC-P8	FBXO39	FMNPYNAVL	78%
		FFFERIMKY	46%

The inventors optimized each dominant PEPI to bind to most HLA class II alleles of most subjects. This should enhance efficacy, because it will induce $CD4^+$ T helper cells that can augment $CD8^+$ CTL responses and contribute to long lasting T cell responses. The example

presented in Figure 4 demonstrates that PEPIs that bind to ≧3 HLA class II alleles most likely activate T helper cells.

The 15-mer peptides selected with the process described here contain both HLA class I and class II binding dominant PEPIs. Therefore, these peptides can induce both CTL and T helper responses in the highest proportion of subjects.

Process:

1. Identification the HLA class II genotype of 400 normal donors*
2. Extension of each 9-mer dominant PEPI (Table 33) on both sides with amino acids that match the source antigen
3. Prediction of HLA class II PEPIs of 400 normal donors using an IEDB algorithm
4. Selection the 15-mer peptide with the highest proportion of subject have HLA Class II binding PEPIs
5. Ensure the presence of one dominant HLA class II PEPI in each vaccine peptide when joining two 15-mer peptides

The 12 optimized 15-mer peptides derived from the 7 CTAs in PolyPEPI1018 are presented in the Table 38. These peptides have different HLA class II binding characteristics. There is a high variability (0% - 100%) in PEPI generation capacity (≧3 HLA binding) among these peptides despite such an optimized personalized vaccine design.

Table 38 Antigen specific HLA class II binding PEPIs in PolyPEPI1018.

Nr.	CRC antigens	Average HLA class II binding alleles	% subjects with ≧1 HLA class II binding	% subjects with ≧2 HLA class II binding	% subjects with ≧3 HLA class II binding	% subjects with ≧4 HLA class II binding
CRC-P1	TSP50 (83-97)	0	0%	0%	0%	0%
	TSP50 (190-204)	**4**	100%	99%	88%	**53%**
CRC-P2	**EPCAM(139-153)**	**5**	100%	100%	100%	**98%**
	SURVIVIN(127-141)	2	84%	58%	26%	11%
CRC-P3	EPCAM(251-265)	0	0%	0%	0%	0%

	MAGE-A8(113-127)	**4**	100%	100%	95%	**72%**
CRC-P6	**CAGE(613-627)**	**5**	100%	100%	99%	**95%**
	SURVIVIN(15-29)	3	100%	97%	83%	45%
CRC-P7	**CAGE(759-773)**	**3**	100%	98%	87%	**56%**
	SPAG9(16-30)	1	66%	35%	9%	2%
CRC-P8	FBXO39(95-109)	3	100%	94%	43%	13%
	FBXO39(284-298)	**5**	100%	100%	100%	**98%**

The 30-mer vaccine peptides have the following advantages compared to shorter peptides:

(i) Multiple precisely selected tumor specific immunogens: each 30 mer contains two precisely selected cancer specific immunogenic peptides that are capable to induce CTL and T helper responses in the majority of the relevant population (similar to the model population).

(ii) Ensure natural antigen presentation. 30-mer long polypeptides can be viewed as pro-drugs: They are not biologically active by themselves, but are processed to smaller peptides (9 to 15 amino acid long) to be loaded into the HLA molecules of professional antigen presenting cells. The antigen presentation resulting from long peptide vaccination reflects physiological pathways for presentation in both HLA class I and class II molecules. In addition, long peptide processing in the cells is much more efficient than that of large intact proteins.

(iii) Exclude induction of tolerizing T cell responses. 9-mer peptides do not require processing by professional antigen-presenting cells and therefore bind exogenously to the HLA class I molecules. Thus, injected short peptides will bind in large numbers to HLA class I molecules of all nucleated cells that have surface HLA class I. In contrast, >20-mers long peptides are processed by antigen presenting cells before binding to HLA class I. Therefore, vaccination with long peptides is less likely to lead to tolerance and will promote the desired antitumor activity.

(iv) Induce long lasting T cell responses because it can stimulate T helper responses by binding to multiple HLA class II molecules

(v) Utility. GMP manufacturing, formulation, quality control and administration of a smaller number of peptides (each with all of the above characteristics) is more feasible than a larger number of peptides supplying different characteristics.

Each 30-mer peptide in PolyPEPI1018 consists of 2 HLA class I binding dominant PEPIs and at least one strong HLA class II binding PEPI. Strong binding PEPIs bind to 4 HLA class II alleles in >50% of individuals. Therefore, the vaccine peptides are tailored to both HLA class I and class II alleles of individual subjects in a general population (which is a relevant population for CRC vaccine design).

As demonstrated above the high HLA genotype variability in subjects results in high variability of T cell responses induced by PolyPEPI1018. This justifies the co-development of a CDx that determines likely responders. The PEPI3+ and >2PEPI3+ biomarkers could predict the immune response and clinical responses, respectively, of subjects vaccinated with PolyPEPI1018 as detailed in Examples 11 and 12. These biomarkers will be used to co-develop a CDx which predicts likely responders to PolyPEPI1018 CRC vaccine.

Example 23 - Analysis of the composition and immunogenicity of PolyPEPI1018 CRC vaccine

Selected peptides for the PolyPEPI1018 composition are as shown in Table 39.

Table 39 - Selected Colorectal Cancer Vaccine peptides for PolyPEPI1018 composition

SEQID	TREOSID	Source Antigen	Peptide (30mer)	HLAI* (CD8)	HLAII** (CD4)
130	CCV1000-5-1	TSP50	PSTTMETQFPVSEGKSRYRAQRFWSWVGQA	53%	88%
121	CCV1000-2-2	EpCAM/Survivin	VRTYWIIIELKHKARTAKKVRRAIEQLAAM	57%	100%
131	CCV1000-5-3	EpCAM /Mage-A8	YVDEKAPEFSMQGLKDEKVAELVRFLLRKY	43%	95%
124	CCV1000-2-6	Cage/Survivin	LASKMHSLLALMVGLKDHRISTFKNWPFLE	58%	99%
134	CCV1000-5-7	Cage/Spag9	PKSMTMMPALFKENRSGAVMSERVSGLAGS	57%	87%
126	CCV1000-2-8	FBXO39	KFMNPYNAVLTKKFQKVNFFFERIMKYERL	90%	100%
			PolyPEPI1018 (6 peptide together)	98%	100%

* Percentage of individuals having CD8+ T cell specific PEPI3+ within the Model Population (n=433).

**Percentage of individuals having CD4+ T cell specific PEPI4+ within normal donors (n=400).

Characterization of immunogenicity

The inventors used the PEPI3+ Test to characterized the immunogenicity of PolyPEPI1018 in a cohort of 37 CRC patients with complete HLA genotype data. T cell responses were predicted in each patient against the same 9 mer peptides that will be used in clinical trials. These peptides represent the 12 dominant PEPI3+ within the PolyPEPI1018 peptides. The 9 mers are shown in Table 39.

The specificity and sensitivity of PEPI3+ prediction depends on the actual number of HLAs predicted to bind a particular epitope. Specifically, the inventors have determined that the probability that one HLA-restricted epitope induces a T cell response in a subject is typically 4%, which explains the poor sensitivity of the state-of-art prediction methods based on HLA restricted epitope prediction. Applying the PEPI3+ methodology, the inventors determined the probability that T cell response to each of the dominant PEPI3+-specific would be induced by PolyPEPI1018 in the 37 CRC patients. The results from this analysis are summarized in the Table 40.

Table 40 Probability of Dominant PEPI in the 6 Peptides of PolyPEPI1018 in 37 CRC Patients

CRC Patient	CRC-P1		CRC-P2		CRC-P3		CRC-P6		CRC-P7		CRC-P8		Expected Number of PEPIs
	TSP50 (83-97)	TSP50 (190-204)	EpCAM (139-153)	Survivin (127-141)	EpCAM (251-265)	MAGEA8 (113-127)	CAGE1 (613-627)	Survivin (15-29)	CAGE1 (759-773)	SPAG9 (16-30)	FBXO39 (95-109)	FBXO39 (284-298)	
CRC-01	22%	4%	22%	4%	22%	22%	**100%**	1%	**98%**	**84%**	**100%**	22%	**5.01**
CRC-02	22%	1%	22%	22%	22%	22%	**100%**	1%	**98%**	22%	**100%**	**98%**	**5.29**
CRC-03	**84%**	22%	**84%**	22%	22%	22%	**84%**	22%	22%	22%	**100%**	22%	**5.29**
CRC-04	22%	**84%**	22%	4%	22%	4%	**98%**	4%	4%	22%	**100%**	**84%**	**4.70**
CRC-05	22%	22%	4%	4%	22%	4%	**98%**	1%	4%	4%	**100%**	**84%**	**3.68**
CRC-06	**84%**	22%	4%	**84%**	**98%**	4%	22%	4%	4%	4%	**100%**	**98%**	**5.27**
CRC-07	22%	22%	22%	22%	22%	4%	**98%**	1%	22%	22%	**100%**	**84%**	**4.41**
CRC-08	22%	22%	22%	**98%**	**84%**	22%	**84%**	22%	22%	22%	**100%**	**84%**	**6.04**
CRC-09	22%	**84%**	**84%**	**84%**	**84%**	22%	**100%**	4%	22%	22%	**98%**	**84%**	**7.10**
CRC-10	4%	**98%**	22%	22%	4%	4%	4%	22%	22%	22%	**98%**	**84%**	**4.06**
CRC-11	22%	22%	4%	4%	22%	4%	**84%**	1%	4%	4%	**98%**	**84%**	**3.53**
CRC-12	**84%**	22%	4%	22%	4%	4%	**84%**	4%	**84%**	4%	**100%**	22%	**4.38**
CRC-13	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	1%	4%	**100%**	**98%**	**5.07**
CRC-14	22%	**84%**	4%	4%	22%	4%	**84%**	1%	4%	4%	**100%**	**84%**	**4.16**
CRC-15	**84%**	22%	22%	22%	22%	4%	**84%**	4%	22%	4%	**100%**	**84%**	**4.74**
CRC-16	4%	**84%**	4%	4%	22%	4%	**84%**	1%	4%	22%	**100%**	**84%**	**4.16**
CRC-17	**84%**	**84%**	4%	**84%**	**84%**	4%	4%	4%	4%	4%	**100%**	22%	**4.82**
CRC-18	**84%**	22%	22%	**84%**	**84%**	4%	22%	22%	4%	4%	**100%**	**84%**	**5.36**
CRC-19	22%	22%	22%	22%	22%	4%	**98%**	4%	22%	22%	**100%**	**84%**	**4.45**
CRC-20	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	4%	4%	**100%**	**98%**	**5.10**
CRC-21	22%	22%	22%	22%	**84%**	22%	**98%**	4%	4%	22%	**100%**	**84%**	**5.06**
CRC-22	22%	**98%**	**84%**	4%	22%	22%	**84%**	22%	**84%**	22%	**98%**	22%	**5.84**

CRC Patient	CRC-P1		CRC-P2		CRC-P3		CRC-P6		CRC-P7		CRC-P8		Expected Number of PEPIs
	TSP50 (83-97)	TSP50 (190-204)	EpCAM (139-153)	Survivin (127-141)	EpCAM (251-265)	MAGEA8 (113-127)	CAGE1 (613-627)	Survivin (15-29)	CAGE1 (759-773)	SPAG9 (16-30)	FBXO39 (95-109)	FBXO39 (284-298)	
CRC-23	**84%**	**84%**	**84%**	**84%**	**84%**	22%	**84%**	**84%**	**84%**	4%	**100%**	**84%**	**8.82**
CRC-24	22%	22%	4%	4%	22%	4%	**84%**	1%	4%	4%	**100%**	**84%**	**3.55**
CRC-25	22%	**84%**	22%	4%	22%	4%	**84%**	4%	22%	4%	**100%**	**84%**	**4.56**
CRC-26	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	4%	4%	**100%**	**84%**	**4.97**
CRC-27	22%	22%	4%	4%	22%	4%	**98%**	1%	4%	4%	**100%**	**84%**	**3.68**
CRC-28	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	4%	4%	**100%**	**98%**	**5.10**
CRC-29	**84%**	**84%**	4%	22%	22%	4%	**84%**	1%	22%	22%	**100%**	**84%**	**5.33**
CRC-30	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	4%	4%	**100%**	**98%**	**5.10**
CRC-31	22%	**84%**	22%	4%	4%	4%	22%	1%	4%	4%	**98%**	**84%**	**3.53**
CRC-32	**84%**	**84%**	4%	**84%**	22%	4%	4%	4%	4%	4%	**98%**	**84%**	**4.80**
CRC-33	**84%**	22%	4%	22%	**84%**	4%	**84%**	1%	4%	4%	**100%**	**98%**	**5.10**
CRC-34	22%	22%	22%	22%	22%	4%	**84%**	1%	22%	4%	**100%**	**84%**	**4.09**
CRC-35	22%	4%	4%	1%	22%	4%	4%	1%	4%	4%	**84%**	**84%**	**2.37**
CRC-36	22%	4%	4%	1%	22%	4%	4%	1%	4%	4%	**84%**	**84%**	**2.37**
CRC-37	22%	4%	4%	1%	22%	4%	4%	1%	4%	4%	**84%**	**84%**	**2.37**

Abbreviations: CRC = colorectal cancer; PEPI = personal epitope

Note: Percentages represent the likelihood of CD8+ T cell Responses Induced by PolyPEPI1018.

Overall, these results show that the most immunogenic peptide in PolyPEPI1018 is CRC-P8, which it is predicted to bind to >3 HLAs in most patients. The least immunogenic peptide, CRC-P3, binds to >1 HLA in many patients and has a 22% chance of inducing T cell responses. Since bioassays used to detect T cell responses are less accurate than PEPI3+, this calculation may be the most accurate characterization of the T cell responses in CRC patients. Though MAGE-A8 and SPAG9 were immunogenic in the Model Population used for vaccine design, MAGE-A8-specific PEPI3+ were absent in the 37 CRC patients, and only one patient (3%) had SPAG9 specific PEPI3+.

Characterization of toxicity – immunoBLAST

A method was developed that can be performed on any antigen to determine its potential to induce toxic immune reaction, like autoimmunity. The method is referred to herein as immunoBLAST. PolyPEPI1018 contains six 30-mer polypeptides. Each polypeptide consists of two 15-mer peptide fragments derived from antigens expressed in CRC. Neoepitopes might be generated in the joint region of the two 15-mer peptides and could induce undesired T cell responses against healthy cells (autoimmunity). This was assesses using the inventors applied the immunoBLAST methodology.

A 16-mer peptide for each of the 30-mer components of PolyPEP1018 was designed. Each 16-mer contains 8 amino acids from the end of the first 15 residues of the 30-mer and 8 amino acids from the beginning of the second 15 residues of the 30-mer – thus precisely spanning the joint region of the two 15-mers. These 16-mers are then analysed to identify cross-reactive regions of local similarity with human sequences using BLAST(https://blast.ncbi.nlm.nih.gov/Blast.cgi), which compares protein sequences to sequence databases and calculates the statistical significance of matches. 8-mers within the 16-mers were selected as the examination length since that length represents the minimum length needed for a peptide to form an epitope, and is the distance between the anchor points during HLA binding.

As shown in Figure 23, the positions of amino acids in a polypeptide are numbered. The start positions of potential 9-mer peptides that can bind to HLAs and form neoepitopes are the 8 amino acids in positions 8-15. The start positions of tumor antigen derived peptides harbored by the 15-mers that can form the pharmaceutically active epitopes are 7+7=14 amino acids at position 1-7 and 16-22. The ratio of possible neoepitope generating peptides is 36.4% (8/22).

The PEPI3+ Test was used to identify neoepitopes and neoPEPI among the 9-mer epitopes in the joint region. The risk of PolyPEPI1018 inducing unwanted T cell responses was assessed in the 433 subjects in the Model Population by determining the proportion of subjects with PEPI3+ among the 9-mers in the joint region. The result of neoepitope/neoPEPI analysis is summarized in table 41. In the 433 subjects of the Model Population, the average predicted epitope number that could be generated by intracellular processing was 40.12. Neoepitopes were frequently generated; 11.61 out of 40.12 (28.9%) epitopes are neoepitopes. Most of the peptides were able to be be identified as a neoepitope, but the number of subjects that present neoepitopes varied.

Epitopes harbored by PolyPEPI1018 create an average of 5.21 PEPI3+. These PEPIs can activate T cells in a subject. The amount of potential neoPEPIs was much lower than neoepitopes (3.7%). There is a marginal possibility that these neoPEPIs compete on T cell activation with PEPIs in some subjects. Importantly, the activated neoPEPI specific T cells had no targets on healthy tissue.

Table 41 - Identification of Potential Neoepitopes of PolyPEPI1018

PolyPEPI1018 Peptide ID:	Potential Neoepitope	Epitope & PEPI3+ binding in 433 Subjects of the Model Population							
		Epitope Binding (1 x HLA)				PEPI3+ binding (3 x HLA)			
		Sub#	Sub%	NeoEPI	NeoEPI count	Sub#	Sub%	NeoPEPI	NeoPEPI count
CRC-P1	QFPVSEGKS	0	0.0%		7	0	0.0%		3
	FPVSEGKSR	160	37.0%	X		1	0.2%	X	
	PVSEGKSRY	150	34.6%	X		0	0.0%		
	VSEGKSRYR	194	44.8%	X		1	0.2%	X	
	SEGKSRYRA	113	26.1%	X		0	0.0%		
	EGKSRYRAQ	77	17.8%	X		0	0.0%		
	GKSRYRAQR	37	8.5%	X		0	0.0%		
	KSRYRAQRF	337	77.8%	X		33	7.6%	X	
CRC-P2	IELKHKART	32	7.4%	X	7	0	0.0%		1
	ELKHKARTA	63	14.5%	X		0	0.0%		
	LKHKARTAK	59	13.6%	X		0	0.0%		
	KHKARTAKK	166	38.3%	X		1	0.2%	X	
	HKARTAKKV	0	0.0%			0	0.0%		
	KARTAKKVR	70	16.2%	X		0	0.0%		
	ARTAKKVRR	134	30.9%	X		0	0.0%		

PolyPEPI1018 Peptide ID:	Potential Neoepitope	Epitope & PEPI3+ binding in 433 Subjects of the Model Population							
		Epitope Binding (1 x HLA)				PEPI3+ binding (3 x HLA)			
		Sub#	Sub%	NeoEPI	NeoEPI count	Sub#	Sub%	NeoPEPI	NeoPEPI count
	RTAKKVRRA	41	9.5%	X		0	0.0%		
CRC-P3	EFSMQGLKD	0	0.0%		5	0	0.0%		1
	FSMQGLKDE	188	43.4%	X		0	0.0%		
	SMQGLKDEK	138	31.9%	X		0	0.0%		
	MQGLKDEKV	16	3.7%	X		0	0.0%		
	QGLKDEKVA	0	0.0%			0	0.0%		
	GLKDEKVAE	0	0.0%			0	0.0%		
	LKDEKVAEL	186	43.0%	X		3	0.7%	X	
	KDEKVAELV	51	11.8%	X		0	0.0%		
CRC-P6	LLALMVGLK	252	58.2%	X	7	0	0.0%		1
	LALMVGLKD	86	19.9%	X		0	0.0%		
	ALMVGLKDH	65	15.0%	X		0	0.0%		
	LMVGLKDHR	97	22.4%	X		0	0.0%		
	MVGLKDHRI	67	15.5%	X		0	0.0%		
	VGLKDHRIS	0	0.0%			0	0.0%		
	GLKDHRIST	4	0.9%	X		0	0.0%		
	LKDHRISTF	195	45.0%	X		5	1.2%	X	
CRC-P7	PALFKENRS	0	0.0%		5	0	0.0%		1
	ALFKENRSG	0	0.0%			0	0.0%		
	LFKENRSGA	41	9.5%	X		0	0.0%		
	FKENRSGAV	114	26.3%	X		0	0.0%		
	KENRSGAVM	261	60.3%	X		0	0.0%		
	ENRSGAVMS	0	0.0%			0	0.0%		
	NRSGAVMSE	227	52.4%	X		0	0.0%		
	RSGAVMSER	197	45.5%	X		2	0.5%	X	
CRC-P8	AVLTKKFQK	181	41.8%	X	7	0	0.0%		3
	VLTKKFQKV	208	48.0%	X		2	0.5%	X	
	LTKKFQKVN	0	0.0%			0	0.0%		
	TKKFQKVNF	25	5.8%	X		0	0.0%		
	KKFQKVNFF	250	57.7%	X		12	2.8%	X	
	KFQKVNFFF	273	63.0%	X		23	5.3%	X	
	FQKVNFFFE	163	37.6%	X		0	0.0%		
	QKVNFFFER	110	25.4%	X		0	0.0%		

Abbreviations: CRC = colorectal cancer; HLA = human leukocytic antigen; PEPI = personal epitope

Each of the 30-mer peptides in PolyPEPI1018 were released for clinical development since none of the 8-mers in the joint regions matched any human protein, except the target CTAs.

Characterisation of activity / efficacy

The inventors have developed pharmacodynamic biomarkers to predict the activity/effect of vaccines in individual human subjects as well as in populations of human subjects. These biomarkers expedite more effective vaccine development and also decrease the development cost. The inventors have the following tools:

Antigen expression knowledgebase: The inventors have collected data from experiments published in peer reviewed scientific journals regarding the tumor antigens expressed by tumor cells and organized by tumor type to create a database of CTA expression levels – CTA database (CTADB). As of April 2017, the CTADB contained data from 145 CTAs from 41,132 tumor specimens, and was organized by the CTA expression frequencies in different types of cancer.

***In silico* trial populations:** The inventors have also collected data on the HLA genotypes of several different model populations. Each individual in the populations has complete 4-digit HLA genotype and ethnicity data. The populations are summarized in Table 42.

Table 42 In silico trial populations

Population	Number of Subjects	Inclusion criteria
Model Population	433	Complete HLA class I genotype Diverse ethnicity
CRC patients	37	Complete HLA class I genotype CRC diagnosis, unknown ethnicity
"Big" Population	7,189	Complete HLA class I genotype Diverse ethnicity
Chinese Population	234	Complete HLA class I genotype Chinese ethnicity
Irish Population	999	Complete HLA class I genotype Irish ethnicity

Abbreviations: CRC = colorectal cancer; HLA = human leukocyte antigen

Using these tools (or potentially equivalent databases or model populations), the following markers can be assessed:

- **AG95 – potency of a vaccine**: The number of antigens in a cancer vaccine that a specific tumor type expresses with 95% probability. AG95 is an indicator of the vaccine's potency, and is independent of the immunogenicity of the vaccine antigens. AG95 is calculated from the tumor antigen expression rate data, which is collected in the CTADB. Technically, AG95

is determined from the binomial distribution of CTAs, and takes into account all possible variations and expression rates. In this study, AG95 was calculated by cumulating the probabilities of a certain number of expressed antigens, by the widest range of antigens where the sum of probabilities was less than or equal to 95%. The correct value isbetween 0 (no expression expected with 95% probability) and maximum number of antigens (all antigens expressed with 95% probability).

- **PEPI3+ count – immunogenicity of a vaccine in a subject**: Vaccine-derived PEPI3+ are personal epitopes that induce T cell responses in a subject. PEPI3+ can be determined using the PEPI3+ Test in subjects who's complete 4-digit HLA genotype is known.
- **AP count – antigenicity of a vaccine in a subject**: Number of vaccine antigens with PEPI3+. Vaccines like PolyPEPI1018 contain sequences from antigens expressed in tumor cells. AP count is the number of antigens in the vaccine that contain PEPI3+, and the AP count represents the number of antigens in the vaccine that can induce T cell responses in a subject. AP count characterizes the vaccine-antigen specific T cell responses of the subject since it depends only on the HLA genotype of the subject and is independent of the subject's disease, age, and medication. The correct value is between 0 (no PEPI presented by the antigen) and maximum number of antigens (all antigens present PEPIs).
- **AP50 – antigenicity of a vaccine in a population**: The mean number of vaccine antigens with a PEPI in a population. The AP50 is suitable for the characterization of vaccine-antigen specific T cell responses in a given population since it depends on the HLA genotype of subjects in a population. Technically, the AP count was calculated in the Model Population and the binomial distribution of the result was used to calculate the AP50.
- **AGP count – effectiveness of a vaccine in a subject**: Number of vaccine antigens expressed in the tumor with PEPI. The AGP count indicates the number of tumor antigens that vaccine recognizes and induces a T cell response against (hit the target). The AGP count depends on the vaccine-antigen expression rate in the subject's tumor and the HLA genotype of the subject. The correct value is between 0 (no PEPI presented by expressed antigen) and maximum number of antigens (all antigens are expressed and present a PEPI).
- **AGP50 – effectiveness of a cancer vaccine in a population**: The mean number of vaccine antigens expressed in the indicated tumor with PEPI (i.e., AGP) in a population. The AGP50 indicates the mean number of tumor antigens that the T cell responses induced by the vaccine can recognize. AGP50 is dependent on the expression rate of the antigens in the indicated

tumor type and the immunogenicity of the antigens in the target population. AGP50 can estimate a vaccine's effectiveness in different populations and can be used to compare different vaccines in the same population. The computation of AGP50 is similar to that used for AG50, except the expression is weighted by the occurrence of the PEPI3+ in the subject on the expressed vaccine antigens. In a theoretical population, where each subject has a PEPI from each vaccine antigen, the AGP50 will be equal to AG50. In another theoretical population, where no subject has a PEPI from any vaccine antigen, the AGP50 will be 0. In general, the following statement is valid: $0 \leq AGP50 \leq AG50$.

- **mAGP – a candidate biomarker for the selection of likely responders:** Likelihood that a cancer vaccine induces T cell responses against multiple antigens expressed in the indicated tumor. mAGP is calculated from the expression rates of vaccine-antigens in CRC and the presence of vaccine derived PEPIs in the subject. Technically, based on the AGP distribution, the mAGP is the sum of probabilities of the multiple AGP (≥2 AGPs).

Application of these markers to assess antigenicity and effectiveness PolyPEPI1018 in Individual Patients with CRC

Table 43 shows the antigenicity and effectiveness of PolyPEPI1018 in 37 CRC patients using AP and AGP50, respectively. As expected from the high variability of PolyPEPI1018 specific T cell responses (see Table 41), the AP and AGP50 have high variability. The most immunogenic antigen in PolyPEPI1018 was FOXO39; each patient had a PEPI3+. However, FOXO39 is expressed only 39% of CRC tumors, suggesting that 61% of patients will have FOXO39 specific T cell responses that do not recognize the tumor. The least immunogenic antigen was MAGE-A8; none of the 37 CRC patients had a PEPI3+ despite the antigen being expressed in 44% of CRC tumors. These results illustrate that both expression and immunogenicity of antigens can be taken into account when determining a cancer vaccine's effectiveness.

AGP50 indicates the mean number of expressed antigens in CRC tumor with PEPIs. Patients with higher AGP50 values are more likely to respond to PolyPEPI1018 since higher AGP50 values indicate that the vaccine can induce T cell responses against more antigens expressed in CRC cells.

The last column in the Table 43 shows the probability of mAGP (multiple AGP; i.e., at least 2 AGPs) in each of the 37 CRC patients. The average mAGP in patients with CRC is 66%, suggesting that there is a 66% likelihood that a CRC patient will induce T cell responses against multiple antigens expressed in the tumor.

Table 43 - Antigenicity (AP count), Effectiveness (AGP50 count), and mAGP of PolyPEPI1018 in 37 CRC Patients

Antigens (CTAs) in PolyPEPI1018	TSP50	EpCAM	Survivin	CAGE1	SPAG9	FBXO39	MAGE-A8	Number of AP (AP count)	Number of AGP50 (AGP50 count)	mAGP
Expression rate	89%	88%	87%	74%	74%	39%	44%			
CRC Patients										
CRC-01	0	0	0	1	1	1	0	3	1.87	90%
CRC-02	0	0	0	1	0	1	0	2	1.13	85%
CRC-03	1	1	0	1	0	1	0	4	2.91	97%
CRC-04	1	0	0	1	0	1	0	3	2.03	91%
CRC-05	0	0	0	1	0	1	0	2	1.13	78%
CRC-06	1	1	1	1	0	1	0	5	3.78	99%
CRC-07	0	0	0	1	0	1	0	2	1.13	84%
CRC-08	0	1	1	1	0	1	0	4	2.89	98%
CRC-09	1	1	1	1	0	1	0	5	3.78	99%
CRC-10	1	0	0	0	0	1	0	2	1.28	86%
CRC-11	0	0	0	1	0	1	0	2	1.13	79%
CRC-12	1	0	0	1	0	1	0	3	2.03	88%
CRC-13	1	1	1	1	0	1	0	5	3.78	98%
CRC-14	1	0	0	1	0	1	0	3	2.03	87%
CRC-15	1	0	0	1	0	1	0	3	2.03	90%
CRC-16	1	0	0	1	0	1	0	3	2.03	85%
CRC-17	1	1	1	0	0	1	0	4	3.04	96%
CRC-18	1	1	1	1	0	1	0	5	3.78	98%
CRC-19	0	0	0	1	0	1	0	2	1.13	85%
CRC-20	1	1	1	1	0	1	0	5	3.78	98%
CRC-21	0	1	0	1	0	1	0	3	2.01	93%
CRC-22	1	1	0	1	0	1	0	4	2.91	97%
CRC-23	1	1	1	1	0	1	0	5	3.78	99%
CRC-24	0	0	0	1	0	1	0	2	1.13	82%
CRC-25	1	0	0	1	0	1	0	3	2.03	89%
CRC-26	1	1	0	1	0	1	0	4	2.91	95%
CRC-27	0	0	0	1	0	1	0	2	1.13	78%
CRC-28	1	1	1	1	0	1	0	5	3.78	98%
CRC-29	1	0	0	1	0	1	0	3	2.03	92%
CRC-30	1	1	1	1	0	1	0	5	3.78	98%
CRC-31	1	0	0	0	0	1	0	2	1.28	80%
CRC-32	1	0	1	0	0	1	0	3	2.15	91%
CRC-33	1	1	1	1	0	1	0	5	3.78	98%
CRC-34	0	0	0	1	0	1	0	2	1.13	82%
CRC-35	0	0	0	0	0	1	0	1	0.39	55%
CRC-36	0	0	0	0	0	1	0	1	0.39	55%
CRC-37	0	0	0	0	0	1	0	1	0.39	55%

Abbreviations: CRC = colorectal cancer; PEPI = personal epitope; CTA = cancer testis antigen; AP = expressed antigens with ≥1 PEPI

These biomarkers have immediate utility in vaccine development and in the routine clinical practice because they do not require invasive biopsies. Antigen expression data can be obtained from achieved tumor specimen and organized in databases. 4-digit HLA genotyping can be done

from a saliva specimen. It is a validated test performed by certified laboratories worldwide for transplantation and paternity testing. These assessments will allow drug developers and physicians to gain deeper insights into the immunogenicity and activity of tumor response and the possible emergence of resistance.

Application of these markers to asses antigenicity and effectiveness PolyPEPI1018 in populations

Antigenicity of PolyPEPI1018 CRC Vaccine in a general population

The antigenicity of PolyPEPI1018 in a subject is determined by the AP count, which indicates the number of vaccine antigens that induce T cell responses in a subject. The AP count of PolyPEPI1018 was determined in each of the 433 subjects in the Model Population using the PEPI Test, and the AP50 count was then calculated for the Model Population.

As shown in Figure 24 the AP50 of PolyPEPI1018 in the Model Population is 3.62. Therefore, the mean number of immunogenic antigens (i.e., antigens with ≥1 PEPI) in PolyPEPI1018 in a general population is 3.62.

Effectiveness of PolyPEPI1018 CRC Vaccine in a general population

Vaccine induced T cells can recognize and kill tumor cells if a PEPI in the vaccine is presented by the tumor cell. The number of AGPs (expressed antigens with PEPI) is an indicator of vaccine effectiveness in an individual, and is dependent on both the potency and antigenicity of PolyPEPI1018. As shown in Figure 25, the mean number of immunogenic CTAs (i.e., AP [expressed antigens with ≥1 PEPI]) in PolyPEPI1018 is 2.54 in the Model Population.

The likelihood that PolyPEPI1018 induces T cell responses against multiple antigens in a subject (i.e., mAGP) in the Model Population is 77%.

Comparison of the PolyPEPI1018 CRC vaccine activities in different populations

Table 44 shows the comparison of the immunogenicity, antigenicity, and effectiveness of PolyPEPI1018 in different populations.

Table 44 - Comparison of Immunogenicity, Antigenicity, and Effectiveness of PolyPEPI1018 in Different Sub-populations

Populations	**Number of subject**	**Number of PEPI3+**		**Number of AP**		**Number of AGP50**	
		Average	**SD**	**Average**	**SD**	**Average**	**SD**

CRC	**37**	5.16	1.98	3.19	1.31	2.21	1.13
Model	**433**	5.02	2.62	3.62	1.67	2.54	1.25
Big	**7,189**	5.20	2.82	3.75	1.74	2.66	1.30
Chinese	**324**	5.97	3.16	4.28	1.78	3.11	1.30
Irish	**999**	3.72	1.92	2.86	1.46	1.94	1.10

Abbreviations: CRC = colorectal cancer; PEPI = personal epitope; SD = standard deviation; AP = expressed antigens with ≥1 PEPI

The average number of PEPI3+ and AP results demonstrate that PolyPEPI1018 is highly immunogenic and antigenic in all populations; PolyPEPI1018 can induce an average of 3.7 – 6.0 CRC specific T cell clones against 2.9 – 3.7 CRC antigens. PolyPEPI1018 immunogenicity was similar in patients with CRC and the average population ($p>0.05$), this similarity may have been due to the small sample size of the CRC population. Additional analyses suggest that PolyPEPI1018 is significantly more immunogenic in a Chinese population compared to an Irish or a general population ($p<0.0001$). The differences in immunogenicity are also reflected in the effectiveness of the vaccine as characterized by AGP50; PolyPEPI1018 is most effective in a Chinese population and less effective in an Irish population. Since a CDx will be used to select likely responders to PolyPEPI1018, ethnic differences will only be reflected in the higher percentage of Chinese individuals that might be eligible for treatment compared with Irish individuals.

Example 24 – Personalised Immunotherapy Composition for treatment of patient with late stage metastatic breast cancerPatient BRC05 was diagnosed with **i**nflammatory breast cancer on the right with extensive lymphangiosis carcinomatose.Inflammatory breast cancer (IBC) is a rare, but aggressive form of locally advanced breast cancer. It's called inflammatory breast cancer because its main symptoms are swelling and redness (the breast often looks inflamed). Most inflammatory breast cancers are invasive ductal carcinomas (begin in the milk ducts). This type of breast cancer is associated with the expression of oncoproteins of high risk Human Papilloma Virus[1]. Indeed, HPV16 DNA was diagnosed in the tumor of this patient.

Patient's stage in 2011 (6 years prior to PIT vaccine treatment)

T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

pN3a: Metastases in ≥ 10 axillary lymph nodes (at least 1 tumor deposit > 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes.

14 vaccine peptides were designed and prepared for patient BRC05 (Table 45). Peptides PBRC05-P01-P10 were made for this patient based on population expression data. The last 3 peptides in the Table 45 (SSX-2, MORC, MAGE-B1) were designed from antigens that expression was measured directly in the tumor of the patient.

Table 45 – Vaccine peptides for patient BRC05

BRC05 vaccine peptides	Target Antigen	Antigen Expression	20mer peptide	MAXHLA Class I	MAXHLA Class II
PBRC05_P1	SPAG9	88%	XXXXXXXXXXXXXXXXXXXX	3	4
PBRC05_P2	AKAP4	85%	XXXXXXXXXXXXXXXXXXXX	3	4
PBRC05_P3	MAGE-A11	59%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P4	NY-SAR-35	49%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P5	FSIP1	49%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P6	NY-BR-1	47%	XXXXXXXXXXXXXXXXXXXX	3	4
PBRC05_P7	MAGE-A9	44%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P8	SCP-1	38%	XXXXXXXXXXXXXXXXXXXX	3	6
PBRC05_P9	MAGE-A1	37%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P10	MAGE-C2	21%	XXXXXXXXXXXXXXXXXXXX	3	3
PBRC05_P11	MAGE-A12	13%	XXXXXXXXXXXXXXXXXXXX	3	4
PBRC05_P12	SSX-2	6%	XXXXXXXXXXXXXXXXXXXX	3	1
PBRC05_P13	MORC	ND	XXXXXXXXXXXXXXXXXXXX	3	4
PBRC05_P14	MAGE-B1	ND	XXXXXXXXXXXXXXXXXXXX	3	3

Note: Bold red means CD8 PEPI, Underline means best binding CD4 allele.

T cell responses were measured cells in peripheral mononuclear cells 2 weeks after the 1st vaccination with the mix of peptides PBRC05_P1, PBRC05_P2, PBRC05_P3, PBRC05_P4, PBRC05_P5, PBRC05_P6, PBRC05_P7.

Table 46 - Antigen specific T cell responses: Number of spots / 300,000 PBMC

Antigen	Stimulant	Exp1	Exp2	Average
SPAG9	PBRC05_P1	2	1	1.5
AKAP4	PBRC05_P2	11	4	7.5
MAGE-A11	PBRC05_P3	26	32	29
NY-SAR-35	PBRC05_P4	472	497	484.5
FSIP1	PBRC05_P5	317	321	319

NY-BR-1	PBRC05_P6	8	12	10
MAGE-A9	PBRC05_P7	23	27	25
None	Negative Control (DMSO)	0	3	1.5

The results show that a single immunization with 7 peptides induced potent T cell responses against 3 out of the 7 peptides demonstrating potent MAGE-A11, NY-SAR-35, FSIP1 and MAGE-A9 specific T cell responses. There were weak responses against AKAP4 and NY-BR-1 and no response against SPAG9.

References

[1] Bagarazzi et al. Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. Science Translational Medicine. 2012; 4(155):155ra138.

[2] Gudmundsdotter et al. Amplified antigen-specific immune responses in HIV-1 infected individuals in a double blind DNA immunization and therapy interruption trial. Vaccine. 2011; 29(33):5558-66.

[3] Bioley et al. HLA class I - associated immunodominance affects CTL responsiveness to an ESO recombinant protein tumor antigen vaccine. Clin Cancer Res. 2009; 15(1):299-306.

[4] Valmori et al. Vaccination with NY-ESO-1 protein and CpG in Montanide induces integrated antibody/Th1 responses and CD8 T cells through cross-priming. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104(21):8947-52.

[5] Yuan et al. Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab.Proc Natl Acad Sci U S A. 2011;108(40):16723-16728.

[6] Kakimi et al. A phase I study of vaccination with NY-ESO-1f peptide mixed with Picibanil OK-432 and Montanide ISA-51 in patients with cancers expressing the NY-ESO-1 antigen.Int J Cancer. 2011;129(12):2836-46.

[7] Wada et al. Vaccination with NY-ESO-1 overlapping peptides mixed with Picibanil OK-432 and montanide ISA-51 in patients with cancers expressing the NY-ESO-1 antigen. J Immunother. 2014;37(2):84-92.

[8] Welters et al. Induction of tumor-specific CD4+ and CD8+ T-cell immunity in cervical cancer patients by a human papillomavirus type 16 E6 and E7 long peptides vaccine. Clin. Cancer Res. 2008; 14(1):178-87.

[9] Kenter et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009; 361(19):1838-47.

[10] Welters et al. Success or failure of vaccination for HPV16-positive vulvar lesions correlates with kinetics and phenotype of induced T-cell responses. PNAS. 2010; 107(26):11895-9.

[11] http://www.ncbi.nlm.nih.gov/projects/gv/mhc/main.fcgi?cmd=initThe MHC database, NCBI (Accessed Mar 7, 2016).

[12] Karkada et al. Therapeutic vaccines and cancer: focus on DPX-0907. Biologics. 2014;8:27-38.

[13] Butts et al. Randomized phase IIB trial of BLP25 liposome vaccine in stage IIIB and IV non-small-cell lung cancer. J Clin Oncol. 2005;23(27):6674-81.

[14] Yuan et al.Safety and immunogenicity of a human and mouse gp100 DNA vaccine in a phase I trial of patients with melanoma.Cancer Immun. 2009;9:5.

[15] Kovjazin et al. ImMucin: a novel therapeutic vaccine with promiscuous MHC binding for the treatment of MUC1-expressing tumors. Vaccine. 2011;29(29-30):4676-86.
[16] Cathcart et al. Amultivalent bcr-abl fusion peptide vaccination trial in patients with chronic myeloid leukemia.Blood. 2004;103:1037-1042.
[17] Chapuis et al. Transferred WT1-reactive CD8+ T cells can mediate antileukemic activity and persist in post-transplant patients. Sci Transl Med. 2013;5(174):174ra27.
[18] Keilholz et al. A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. Blood; 2009; 113(26):6541-8.
[19] Walter et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med. 2012;18(8):1254-61.
[20] Phuphanich et al. Phase I trial of a multi-epitope-pulsed dendritic cell vaccine for patients with newly diagnosed glioblastoma. Cancer Immunol Immunother. 2013;62(1):125-35.
[21] Kantoff et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol. 2010;28(7):1099-105.
[22] Tagawa et al. Phase I study of intranodal delivery of a plasmid DNA vaccine for patients with Stage IV melanoma. Cancer. 2003;98(1):144-54.
[23] Slingluff et al. Randomized multicenter trial of the effects of melanoma-associated helper peptides and cyclophosphamide on the immunogenicity of a multipeptide melanoma vaccine.J Clin Oncol. 2011;29(21):2924-32.
[24] Kaida et al. Phase 1 trial of Wilms tumor 1 (WT1) peptide vaccine and gemcitabine combination therapy in patients with advanced pancreatic or biliary tract cancer. J Immunother. 2011;34(1):92-9.
[25]Fenoglio et al. A multi-peptide, dual-adjuvant telomerase vaccine (GX301) is highly immunogenic in patients with prostate and renal cancer. Cancer Immunol Immunother; 2013; 62:1041–1052.
[26]Krug et al. WT1 peptide vaccinations induce CD4 and CD8 T cell immune responses in patients with mesothelioma and non-small cell lung cancer. Cancer Immunol Immunother; 2010; 59(10):1467-79.
[27]Slingluff et al. Clinical and immunologic results of a randomized phase II trial of vaccination using four melanoma peptides either administered in granulocyte-macrophage colony-stimulating factor in adjuvant or pulsed on dendritic cells. J Clin Oncol; 2003; 21(21):4016-26.
[28]Hodi et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med; 2010;363(8):711-23.
[29] Carmon et al. Phase I/II study exploring ImMucin, a pan-major histocompatibility complex, anti-MUC1 signal peptide vaccine, in multiple myeloma patients. Br J Hematol. 2014; 169(1):44-56.
[30]http://www.merckgroup.com/en/media/extNewsDetail.html?newsId=EB4A46A2AC4A52E7C1257AD9001F3186&newsType=1(Accessed Mar 28, 2016)
[31] Trimble et al. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial. Lancet. 2015;386(10008):2078-88.
[32]Cusi et al. Phase I trial of thymidylate synthase poly epitope peptide (TSPP) vaccine in advanced cancer patients. Cancer Immunol Immunother; 2015; 64:1159–1173.
[33]Asahara et al. Phase I/II clinical trial using HLA-A24-restricted peptide vaccine derived from KIF20A for patients with advanced pancreatic cancer. J Transl Med; 2013;11:291.

[34]Yoshitake et al. Phase II clinical trial of multiple peptide vaccination for advanced head and neck cancer patients revealed induction of immune responses and improved OS. Clin Cancer Res; 2014;21(2):312-21.

[35]Okuno et al. Clinical Trial of a 7-Peptide Cocktail Vaccine with Oral Chemotherapy for Patients with Metastatic Colorectal Cancer. Anticancer Res; 2014; 34: 3045-305.

[36]Rapoport et al. Combination Immunotherapy after ASCT for Multiple Myeloma Using MAGE-A3/Poly-ICLC Immunizations Followed by Adoptive Transfer of Vaccine-Primed and Costimulated Autologous T Cells. Clin Cancer Res; 2014; 20(5): 1355–1365.

[37]Greenfield et al. A phase I dose-escalation clinical trial of a peptidebased human papillomavirus therapeutic vaccine with Candida skin test reagent as a novel vaccine adjuvant for treating women with biopsy-proven cervical intraepithelial neoplasia 2/3. Oncoimmunol; 2015; 4:10, e1031439.

[38] Snyder et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014; 371(23):2189-99.

[39] Van Allen et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science; 2015; 350:6257.

[40] Li et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood; 2001; 98:3241-3248

[41] Takedatsu et al. Determination of Thrombopoietin-Derived Peptides Recognized by Both Cellular and Humoral Immunities in Healthy Donors and Patients with Thrombocytopenia. 2005; 23(7): 975-982

[42] Eisenhauer et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer; 2009; 45(2):228-47.

[43] Therasse et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst; 2000; 92:205-216.

[44] Tsuchida & Therasse. Response evaluation criteria in solid tumors (RECIST): New guidelines. Med Pediatr Oncol. 2001; 37:1-3.

[45] Durie et al. International uniform response criteria for multiple myeloma. Leukemia; 2006;20:1467–1473.

CLAIMS

1. A method of predicting the cytotoxic T cell response rate and/or the helper T cell response rate of a specific or target human population to administration of a polypeptide, or to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, the method comprising

(i) selecting or defining a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and/or HLA class II genotype;

(ii) determining for each subject in the model human population whether the polypeptide or polypeptides together comprise

(a) at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; and/or

(b) at least one amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

(iii) predicting

A. the cytotoxic T cell response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(a) predicts a higher cytotoxic T cell response rate in said human population; and/or

B. the helper T cell response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(b) predicts a higher helper T cell response rate in said human population.

2. A method of predicting the clinical response rate of a specific or target human population to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, the method comprising

(i) selecting or defining a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype;

(ii) determining

(a) for each subject in the model human population whether the one or more active ingredient polypeptides together comprise at least two different amino acid sequences each of which is a T cell epitope capable of binding to at least two HLA class I molecules of the subject, optionally wherein the at least two different amino acid

sequences are comprised in the amino acid sequence of two different polypeptide antigens targeted by the active ingredient polypeptide(s);

(b) in the model population the mean number of target polypeptide antigens that comprise at least one amino acid sequence that is

A. a T cell epitope capable of binding to at least three HLA class I molecules of the individual subjects of the model population; and

B. comprised in the amino acid sequence of the active ingredient polypeptide(s); and/or

(c) in the model population the mean number of expressed target polypeptide antigens that comprise at least one amino acid sequence that is

A. a T cell epitope capable of binding to at least three HLA class I molecules of the individual subjects of the model population; and

B. comprised in the amino acid sequence of the active ingredient polypeptide(s); and

(iii) predicting the clinical response rate of said human population, wherein a higher proportion of the model human population meeting the requirements of step (ii)(a), or a higher mean number of target polypeptides in step (ii)(b), or or a higher mean number of expressed target polypeptides in step (ii)(c) predicts a higher clinical response rate in said human population.

3. The method of claim 1 or claim 2 further comprising repeating the method for one or more further polypeptides, pharmaceutical compositions, kits or panels of polypeptides, and ranking the polypeptides, pharmaceutical compositions, kits or panels of polypeptides according to their predicted cytotoxic T cell, helper T cell and/or or clinical response rates in said specific or target human population.

4. The method of any one of claims 1 to 3 further comprising selecting or recommending treatment of a subject in need thereof by administration of one or more polypeptides or pharmaceutical compositions or the polypeptides of one or more kits or panels of polypeptides, based on their predicted response rate or response rate ranking.

5. The method of claim 4, wherein

(a) a polypeptide, pharmaceutical composition, kit or panel of polypeptides having a high predicted response rate or response rate ranking is selected or recommended for inducing a therapeutic immune response in the subject; or

(b) a polypeptide, pharmaceutical composition, kit or panel of polypeptides having a low predicted response rate or response rate ranking is selected or recommended for avoiding a toxic immune response.

6. The method of claim 4 or claim 5 further comprising administering one or more of the selected or recommended polypeptides or pharmaceutical compositions or the polypeptides of one or more kits or panels of polypeptides to the subject.

7. A method of treatment of a human subject in need thereof, the method comprising administering to the subject one or more polypeptides or pharmaceutical compositions that have been selected or recommended for treatment of the subject using a method according to claim 4 or claim 5.

8. A method of designing or preparing a polypeptide, or a polynucleic acid that encodes a polypeptide, for use in a method of inducing an immune response in a subject of a specific or target human population, the method comprising

(i) selecting or defining

(a) a relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and/or by HLA class II genotype; or

(b) one relevant model human population comprising a plurality of subjects each defined by HLA class I genotype and one relevant model human population comprising a plurality of subjects each defined by HLA class II genotype;

(ii) identifying a fragment of up to 50 consecutive amino acids of a target polypeptide antigen that comprises or consists of

A. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of the individual subjects;

B. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of the individual subjects; or

C. a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class I genotype, of binding to at least three HLA class I molecules of the individual subjects and a T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three HLA class II molecules of the individual subjects;

(iii) if the polypeptide fragment selected in step (ii) is an HLA class I–binding epitope, optionally selecting a longer fragment of the target polypeptide antigen, which longer fragment comprises or consists of an amino acid sequence that

F. comprises the fragment selected in step (ii); and

G. is an HLA class II molecule-binding T cell epitope capable, in a high percentage of the subjects of a model population selected or defined in step (i) that is defined by HLA class II genotype, of binding to at least three, or the most possible HLA class II molecules of the individual subjects; and

(iv) designing or preparing a polypeptide, or a polynucleic acid that encodes a polypeptide that comprises one or more polypeptide fragments identified in step (ii) or step (iii), optionally wherein the polypeptide fragment is flanked at the N and/or C terminus by additional amino acids that are not part of the sequence of the target polypeptide antigen.

9. The method of claim 8, comprising identifying one or more further fragments of the same or one or more different target polypeptide antigens, wherein each polypeptide fragment is a T cell epitope capable of binding to at least three HLA class I molecules or at least three HLA class II molecules of at least one subject in the model population; and ranking the fragments by

(i) the percentage of subjects in the model population that express at least three HLA class I molecules capable of binding to the fragment;

(ii) the percentage of subjects in the model population that are predicted to express both the target polypeptide antigen comprising the fragment and at least three HLA class I molecules capable of binding to the fragment;

(iii) the percentage of subjects in the model population that express at least three HLA class II molecules capable of binding to the fragment;

(iv) the percentage of subjects in the model population that are predicted to express both

the target polypeptide antigen comprising the fragment and at least three HLA class II molecules capable of binding to the fragment;

(v) the percentage of subjects in the model population that express at least three HLA class I molecules and at least three HLA class II molecules capable of binding to the fragment; or

(iv) the percentage of subjects in the model population that are predicted to express both the target polypeptide antigen comprising the fragment and at least three HLA class I molecules and at least three HLA class II molecules capable of binding to the fragment.

10. The method of claim 9, which comprises selecting one or more of the polypeptide fragments based on their ranking, and designing or preparing the polypeptide to comprise or the polynuceic acid to encode the one of more selected polypeptide fragments.

11. The method of any one of claims 8 to 10, further comprising designing or preparing a polypeptide, a panel of polypeptides, or a pharmaceutical composition or kit comprising one or more polypeptides as active ingredients for use in a method of inducing an immune response in a subject of the specific or target human population, wherein the polypeptide(s) or active ingredient polypeptides comprises at least two polypeptide fragments, optionally between 2 and 15 polypeptide fragments, selected according to the method of claim 8 or claim 10.

12. The method of claim 11, wherein the two or more or each of the fragments are from different target polypeptide antigens, optionally different target polypeptide antigens selected from the antigens listed in Tables 2 to 6 and/or different cancer associated antigens, optionally wherein one or more or each of the cancer associated antigens are CTAs.

13. The method of claim 11 or claim 12, wherein two or more or each of the fragments are arranged in the polypeptide end to end.

14. The method of claim 13, further comprising screening all of the neoepitopes formed at the join between any two of the selected polypeptide fragments arranged end to end in a

single polypeptide to eliminate peptides comprising a neoepitope amino acid sequence that

(i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

(ii) is a T cell epitope capable of binding, in more than a threshold percentage of human subjects, to at least two HLA class I molecules expressed by individual subjects;

(i) meets both requirements (i) and (ii).

15. The method of any of claims 8 to 14, wherein the one or more polypeptides have been screened to eliminate polypeptides comprising an amino acid sequence that
(i) corresponds to a fragment of a human polypeptide expressed in healthy cells; or
(ii) corresponds to a fragment of a human polypeptide expressed in healthy cells and is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

16. A method of inducing an immune response in a subject of a specific or target human population, the method comprising designing or preparing a polypeptide, a panel of polypeptides, a polynucleic acid encoding a polypeptide, or a pharmaceutical composition or kit for use in said specific or target human population according to the method of any one of claims 8 to 15 and administering the polypeptide(s), polynucleic acid, pharmaceutical composition or the active ingredient polypeptides of the kit to the subject.

17. A polypeptide, panel of polypeptides, polynucleic acid, pharmaceutical composition or kit for use in a method of inducing an immune response in a subject of a specific or target human population, wherein the polypeptide, panel of polypeptides, polynucleic acid, pharmaceutical composition or kit is designed or prepared according to the method of any one of claims 8 to 16 for use in said specific or target human population, and wherein the composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

18. A pharmaceutical composition, panel of polypeptides or kit for use in a method of inducing an immune response in a subject of a specific or target human population,

wherein the pharmaceutical composition, panel of polypeptides or kit comprises as active ingredients a first and a second and optionally one or more additional polypeptides, wherein each polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of subjects in the specific or target population, wherein the T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

19. A pharmaceutical composition, panel of polypeptides or kit for use in a method of inducing an immune response in a human subject, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first region and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of at least 10% of subjects in the specific or target population, wherein the T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

20. The pharmaceutical composition, panel of polypeptides or kit for use of claim 18 or 19, wherein the amino acid sequence of one or more or each of the T cell epitopes is from a polypeptide selected from the antigens listed in Tables 2 to 6, or is a cancer associated antigen, optionally wherein one or more or each of the cancer associated antigens is a CTA.

21. The pharmaceutical composition, panel of polypeptides or kit for use of claims 18 to 20, wherein the amino acid sequence of two or more or each of the T cell epitopes is from a different polypeptide selected from the antigens listed in Tables 2 to 6, and/or different cancer associated antigens, optionally wherein one or more or each of the cancer associated antigens are CTAs.

22. A pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer in a subject in need thereof, wherein the pharmaceutical composition, panel of

polypeptides or kit comprises as active ingredients a first and a second peptide and optionally one or more additional peptides, wherein each peptide comprises an amino acid sequence that is an HLA class I-binding T cell epitope wherein at least 10% of human subjects having cancer both

iii. express a tumor associated antigen selected from the antigens listed in Table 2 that comprises said T cell epitope; and

iv. have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional peptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

23. A pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer in a subject in need thereof, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is an HLA class I-binding T cell epitope wherein at least 10% of human subjects having cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional regions are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

24. A pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer selected from colorectal, breast, ovarian, melanoma, non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma in a subject in need thereof, wherein the pharmaceutical composition, panel of polypeptides or kit comprises as active ingredients a first and a second polypeptide and optionally one or more additional polypeptides, wherein each

polypeptide comprises an amino acid sequence that is an HLA class I-binding T cell epitope wherein at least 10% of human subjects having said cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional peptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

25. A pharmaceutical composition, panel of polypeptides or kit for use in a method treating a cancer selected from colorectal, breast, ovarian, melanoma, non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma in a subject in need thereof, wherein the pharmaceutical composition, panel of polypeptides or kit comprises an active ingredient polypeptide comprising a first and a second region and optionally one or more additional regions, wherein each region comprises an amino acid sequence that is an HLA class I-binding T cell epitope wherein at least 10% of human subjects having said cancer both

(a) express a tumor associated antigen selected from the antigens listed in Table 2 that comprises said T cell epitope; and

(b) have at least three HLA class I molecules capable of binding to said T cell epitope;

wherein said T cell epitope of the first, second and optionally any additional polypeptides are different from each other, and wherein the pharmaceutical composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

26. A method of treatment of a human subject in need thereof, the method comprising administering to the subject a polypeptide, a panel of polypeptides, a pharmaceutical composition or the active ingredient polypeptides of a kit according to any one of claims 17 to 25, wherein the subject has been determined to express at least three HLA class I molecules and/or at least three HLA class II molecules capable of binding to the

polypeptide or to one or more of the active ingredient poypeptides of the pharmaceutical composition or kit.

27. The method of claim 26, wherein the subject has been determined to express at least three HLA class I and/or at least three HLA class II molecules capable of binding to a threshold minimal number of different T cell epitopes of the polypeptide, or the active ingredient poypeptides of the pharmaceutical composition or kit.

28. The method of claim 26 or claim 27 wherein the active ingredient polypeptides of the pharmaceutical composition, kit or panel of polypeptides have been determined to together comprise at least two different sequences each of which is a T cell epitope capable of binding to at least three HLA class I molecules of the subject, optionally wherein the at least two different amino acid sequences are comprised in the amino acid sequence of two different polypeptide antigens targeted by the active ingredient polypeptide(s) .

29. The method of any one or claims 26 to 28 wherein the pharmaceutical composition has been determined to have higher than a threshold minimum likelihood of inducing a clinical response in the subject, wherein one or more of the following factors corresponds to a higher likelihood of clinical response:

(a) presence in the active ingredient polypeptide(s) of a higher number of amino acid sequences and/or different amino acid sequences that are each a T cell epitope capable of binding to at least three HLA class I of the subject;

(b) a higher number of target polypeptide antigens, comprising at least one amino acid sequence that is both

A. comprised in an active ingredient polypeptide; and

B. a T cell epitope capable of binding to at least three HLA class I of the subject;

optionally wherein the target polypeptide antigens are expressed in the subject, further optionally wherein the target polypeptides antigens are in one or more samples obtained from the subject;

(c) a higher probability that the subject expresses target polypeptide antigens, optionally a threshold number of the target polypeptide antigens and/or optionally target polypeptide

antigens that have been determined to comprise at least one amino acid sequence that is both

A. comprised in in an active ingredient polypeptide; and

B. a T cell epitope capable of binding to at least three HLA class I of the subject; and/or

(d) a higher number of target polypeptide antigens that the subject is predicted to express, optionally a higher number of target polypeptide antigens that the subject expresses with a threshold probability, and/or optionally the target polypeptide antigens that have been determined to comprise at least one amino acid sequence that is both

A. comprised in in an active ingredient polypeptide; and

B. a T cell epitope capable of binding to at least three HLA class I of the subject.

30. The method of claim 29, wherein the likelihood of a clinical response has been determined by a method comprising

(i) identifying which polypeptide antigens targeted by the active ingredient polypeptide(s) comprise an amino acid sequence that is both

A. comprised in in an active ingredient polypeptide; and

B. a T cell epitope capable of binding to at least three HLA class I of the subject;

(ii) using population expression data for each antigen identified in step (i) to determine the probability that the subject expresses one or more of the antigens identified in step (i) that together comprise at least two different amino acid sequences of step (i); and

(iii) determining the likelihood that the subject will have a clinical response to administration of the administration of the pharmaceutical composition, kit or panel of polypeptides, wherein a higher probability determined in step (ii) corresponds to a more likely clinical response.

31. A system comprising

(a) a storage module configured to store data comprising the class I and/or class II HLA genotypes of each subject of a model population of human subjects; and the amino acid sequence of one or more test polypeptides; wherein the model population is representative of a test target human population; and

(b) a computation module configured to identify and/or quantify the amino acid sequences in the one or more test polypeptides that are capable of binding to

multiple class I HLA molecules of each subject in the model population and/or the amino acid sequences in the one or more test polypeptides that are capable of binding to multiple class II HLA molecules of each subject in the model population.

32. The system of claim 31 further comprising

(c) an output module configured to display

(i) a prediction of the cytotoxic T cell response rate and/or the helper T cell response rate of the test target human population to administration of the one or more polypeptides, or one or more pharmaceutical compositions comprising the one or more polypeptides as active ingredients; or

(ii) a prediction of the clinical response rate of the test target human population to a method of treatment comprising administration of one or more pharmaceutical compositions comprising the one or more polypeptides as active ingredients.

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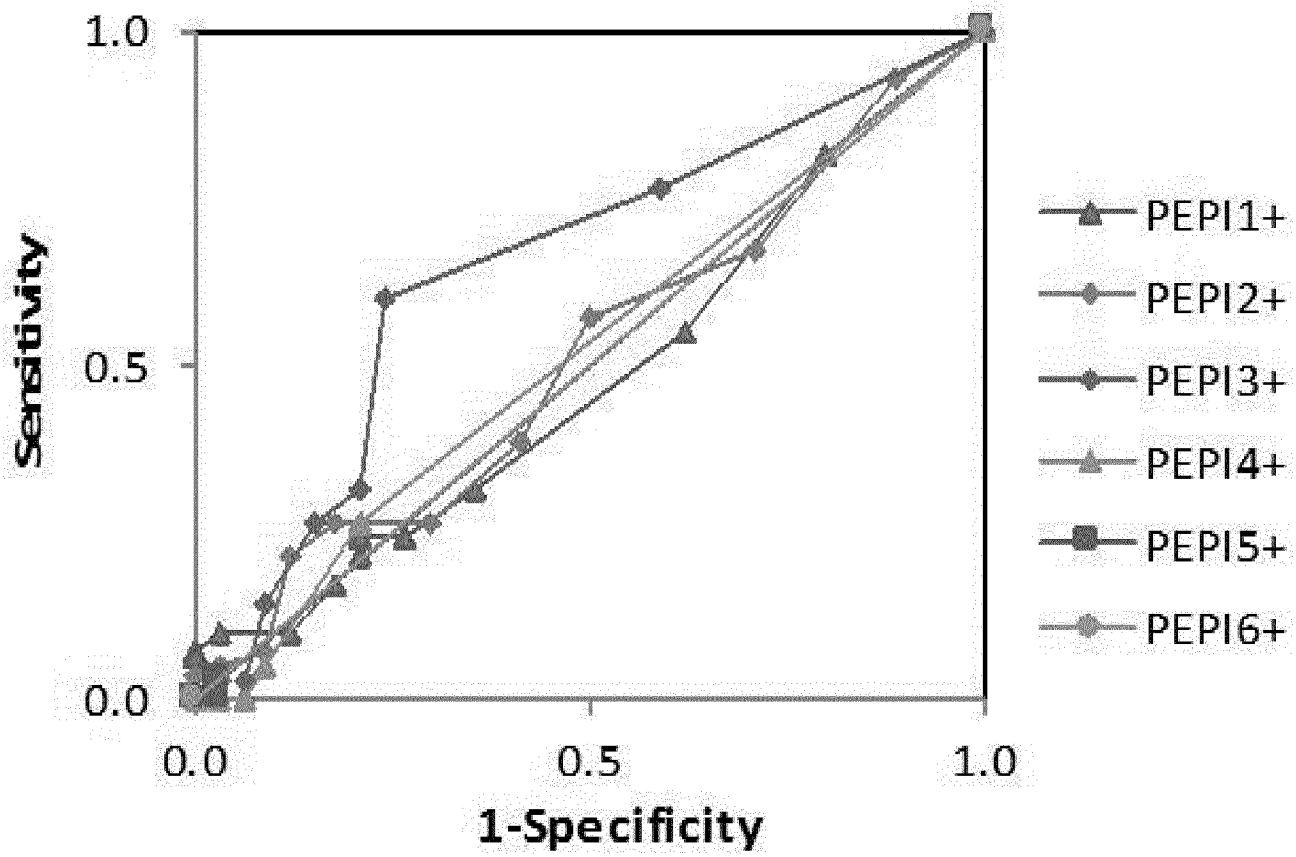
Figure 1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0.0
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PEPI2+
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PEPI5+
PEPI6+

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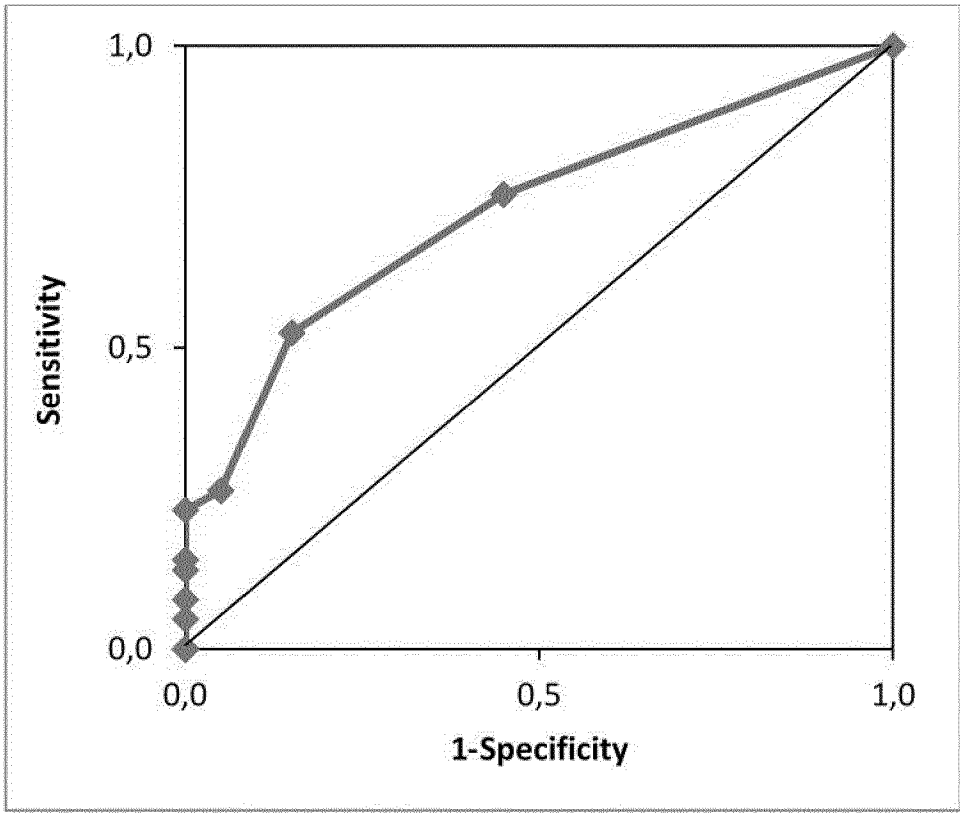
Figure 2



3/25

Figure 3

A

Patient ID	#epitope / HPV-16 E6 Pools															#epitope / HPV-16 E7 Pools								
	1-19	11-29	21-39	31-49	41-59	51-69	61-79	71-89	81-99	91-109	101-119	111-129	121-139	131-149	141-158	1-19	11-29	21-39	31-49	41-59	51-69	61-79	71-89	81-98
1	TN	TN	TN	FN	TN	FP	TN	TN	TN	TN	FN	TN	TN	TN	TN	FP	TN	TN	TN	FP	TN	TN	TN	TN
2	FN	FN	TN	TN	TN	FP	TN	TN	TN	TN	TN	TN	TN	TN	TN	FP	TN	TN	TN	FP	TN	TN	TN	TN
3	TN	TN	TN	TN	TN	TP	TN	TN	TN	TN	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
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22	TN	FN	TN	TN	TN	TP	TN	TN	TN	TN	TN	TN	TN	TN	TN	FP	TN	TN	TN	FP	TN	TN	TN	TN
23	TN	TN	TN	FN	TN	TN	TN	TN	TN	FN	TN	TN	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
27	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
28	TN	TN	TN	TN	TN	FP	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	FP	TN	TN	TN	TN
29	FN	TN	FN	TN	TN	TN	TN	TN	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
30	TN	TN	TN	TN	TN	FP	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
100	TN	TN	TN	TN	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
102	TN	TN	TN	TN	TN	TP	TN	TN	FP	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	FN	TN	TN	TN
103	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN
105	TN	TN	TN	TN	TN	TP	FN	TN	TN	TN	TN	TN	TN	TN	TN	FP	TN	TN	TN	FP	TN	TN	TN	TN
107	TN	TN	TN	TN	TN	TN	TN	TN	TN	FN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	FN	TN

B

Patient ID	#epitope / HPV-16 E6 Pools															#epitope / HPV-16 E7 Pools								
	1-19	11-29	21-39	31-49	41-59	51-69	61-79	71-89	81-99	91-109	101-119	111-129	121-139	131-149	141-158	1-19	11-29	21-39	31-49	41-59	51-69	61-79	71-89	81-98
1	TN	FP	FP	TP	FP	FP	FP	FP	FP	FP	TP	FP	TN	TN	FP	FP	FP	TN	TN	FP	FP	FP	FP	FP
2	TP	TP	FP	FP	FP	FP	FP	FP	FP	FP	TN	TN	TN	FP	FP	FP	FP	TN	TN	FP	TN	FP	FP	FP
3	FP	FP	TN	FP	FP	TP	TN	FP	FP	FP	FP	TP	TN	FP	FP	FP	TN	TN	TN	FP	TN	TN	FP	FP
6	FP	FP	FP	FN	FP	FP	FP	FP	FP	FP	FN	TN	TN	TN	TN	FP	FP	TN	FP	FP	TN	FP	FP	FP
7	FP	FP	FP	FP	FP	TP	TN	FP	FP	FP	FP	FP	TN	FP	FP	FP	TN	TN	TN	FP	TN	TN	FP	FP
8	FP	TP	TN	TP	FP	TP	FP	FP	FP	FP	TP	FP	FP	FP	TP	FP	FP	TN	TN	TP	TN	FP	FP	FP
9	FP	FP	TN	FP	TP	TP	TN	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	TN	FP	TN	FP	FP	FP
10	FP	FP	TN	FP	FP	TP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	TN	TN	TN	FP	TN	TN	FP	FP
11	FP	TP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	TN	FP	TN	TN	FP	FP
13	FP	FP	FP	FP	FP	TP	FP	FP	FP	TP	FP	FP	TN	FP	FP	FP	FP	TN	TN	FP	FP	TN	FP	FP
16	FP	FP	FP	FP	TN	TP	TN	FP	FP	TP	FP	TN	TN	FP	FP	FP	FP	TN	FP	FP	TN	FP	FP	FP
18	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	TN	TP	FP	FP	FP	FP
22	FP	TP	FP	FP	FP	TP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	TN	FP	TN	FP	FP	FP
23	TN	FP	FP	TP	FP	FP	FP	FP	FP	TP	FP	FP	TN	TP	FP	FP	FP	TN	FP	FP	FP	TN	FP	FP
27	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	TN	FP	TN	FP	FP	FP
28	FP	FP	TN	TN	FP	FP	FP	FP	FP	FP	TN	FP	TN	FP	FP	FP	TN	TN	TN	FP	FP	TN	FP	FP
29	TP	FP	TP	FP	FP	FP	FP	FP	FP	TP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	FP	FP
30	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	TN	TN	FP	FP	FP	TN	TN	FP	FP	TN	FP	FP
100	FP	FP	FP	FP	FP	TP	FP	FP	FP	FP	TN	TN	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	TN
102	FP	FP	FP	FP	FP	TP	FP	FP	FP	FP	TN	FP	FP	FP	FP	FP	FP	TN	TN	FP	FN	TN	FP	TN
103	FP	TP	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	TN	TN	FP	TN	TN	FP	FP
105	FP	FP	FP	FP	FP	TP	TP	FP	FP	FP	TN	FP	TN	FP	FP	FP	FP	TN	TN	FP	TN	FP	FP	FP
107	FP	FP	FP	FP	FP	FP	FP	FP	FP	FP	TN	FP	FP	FP	FP	FP	FP	TN	FP	FP	TN	FP	TP	FP

Figure 4

A

Pat ID	#PEPI / HPV-16 E6				E7	
	E6.1	E6.2	E6.3	E6.4	E7.1	E7.2
1	FP	TP	TP	FN	TN	FN
2	FP	TP	TP	TN	TN	TP
3	TP	TP	TP	TP	TN	TP
6	TP	TP	TP	FN	TP	TP
7	TP	TP	TP	TP	TN	TP
8	TP	TP	TP	FN	FP	TP
9	TP	TP	TP	FN	FP	TP
10	FP	TP	TP	FN	TN	TP
11	TP	TP	FN	FN	TN	TP
13	TP	TP	FN	FN	TN	FN
16	TP	TP	TP	FN	FP	TP
18	FP	TP	FN	FN	FN	TP
22	TP	TP	TP	FN	FN	FN
23	FP	TP	TP	FN	TN	TN
27	TP	TP	TP	FN	FN	FN
28	TP	TP	TP	FN	TN	FN
29	FP	TP	TP	FN	FP	TP
30	FP	FP	TN	TN	FN	FN
100	TP	TP	TP	FN	TN	TP
102	TP	TP	TP	FN	FN	TP
103	TP	TP	TP	FN	TN	TN
105	TP	TP	TP	TP	TN	TN
107	TP	TP	FN	FN	TN	FN

B

Patient ID	# epitope / HPV-16 E6&E7 pools					
	E6.1	E6.2	E6.3	E6.4	E7.1	E7.2
1	FP	TP	TP	FN	FP	TP
2	FP	TP	TP	TN	TN	TP
3	TP	TP	TP	FN	FP	TP
6	TP	TP	TP	FN	TP	TP
7	TP	TP	TP	FN	FP	TP
8	TP	TP	TP	FN	FP	TP
9	TP	TP	TP	FN	FP	TP
10	FP	TP	TP	FN	FP	TP
11	TP	TP	TP	FN	FP	TP
13	TP	TP	TP	FN	TN	TP
16	TP	TP	TP	FN	TN	TP
18	FP	TP	TP	FN	FN	TP
22	TP	TP	TP	FN	TP	TP
23	FP	TP	TP	FN	FP	FP
27	TP	TP	TP	FN	TP	TP
28	TP	TP	TP	FN	FP	TP
29	FP	TP	TP	FN	FP	TP
30	FP	FP	FP	TN	FN	TP
100	TP	TP	TP	FN	FP	TP
102	TP	TP	TP	FN	TP	TP
103	TP	TP	TP	FN	TN	FP
105	TP	TP	TP	FN	TN	FP
107	TP	TP	TP	FN	FP	TP

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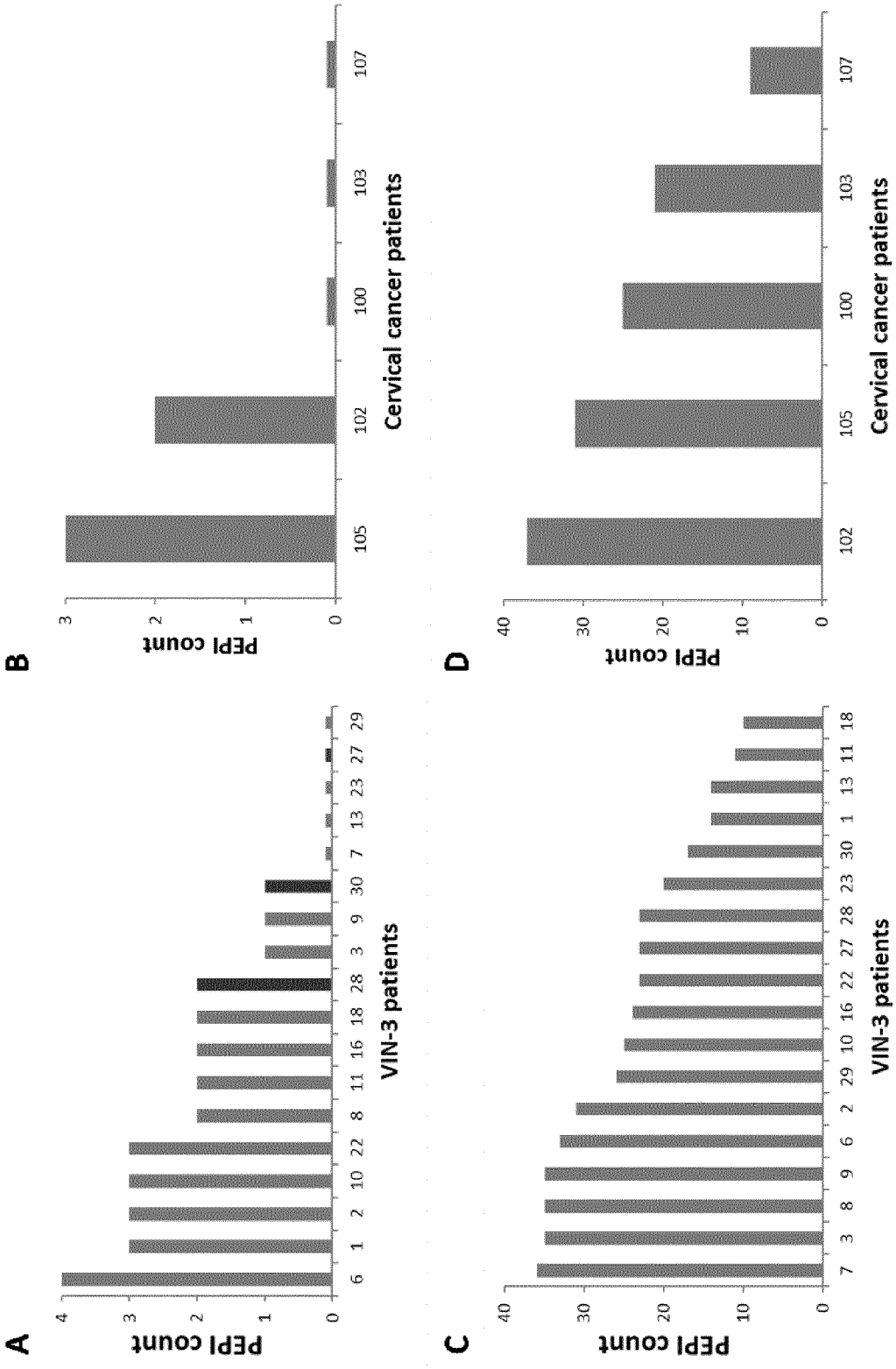
Figure 5


A
PEPI count
VIN-3 patients
B
PEPI count
Cervical cancer patients
C
PEPI count
VIN-3 patients
D
PEPI count
Cervical cancer patients

6/25

Figure 6

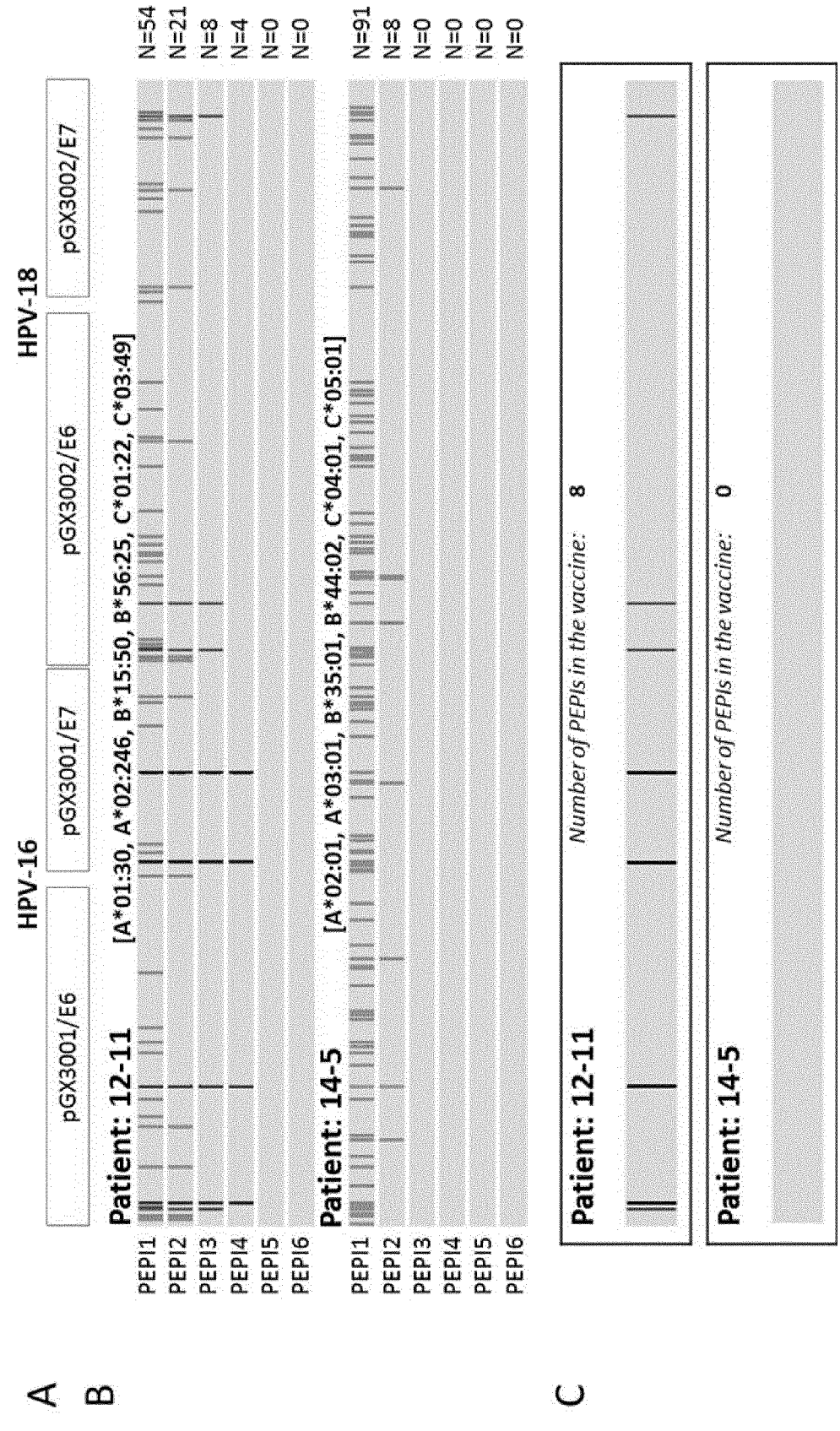

A
B
C
HPV-16
HPV-18
pGX3001/E6
pGX3001/E7
pGX3002/E6
pGX3002/E7
Patient: 12-11
[A*01:30, A*02:246, B*15:50, B*56:25, C*01:22, C*03:49]
N=54
N=21
N=8
N=4
N=0
N=0
PEPI1
PEPI2
PEPI3
PEPI4
PEPI5
PEPI6
Patient: 14-5
[A*02:01, A*03:01, B*35:01, B*44:02, C*04:01, C*05:01]
N=91
N=8
N=0
N=0
N=0
N=0
Patient: 12-11
Number of PEPIs in the vaccine: 8
Patient: 14-5
Number of PEPIs in the vaccine: 0

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Figure 7

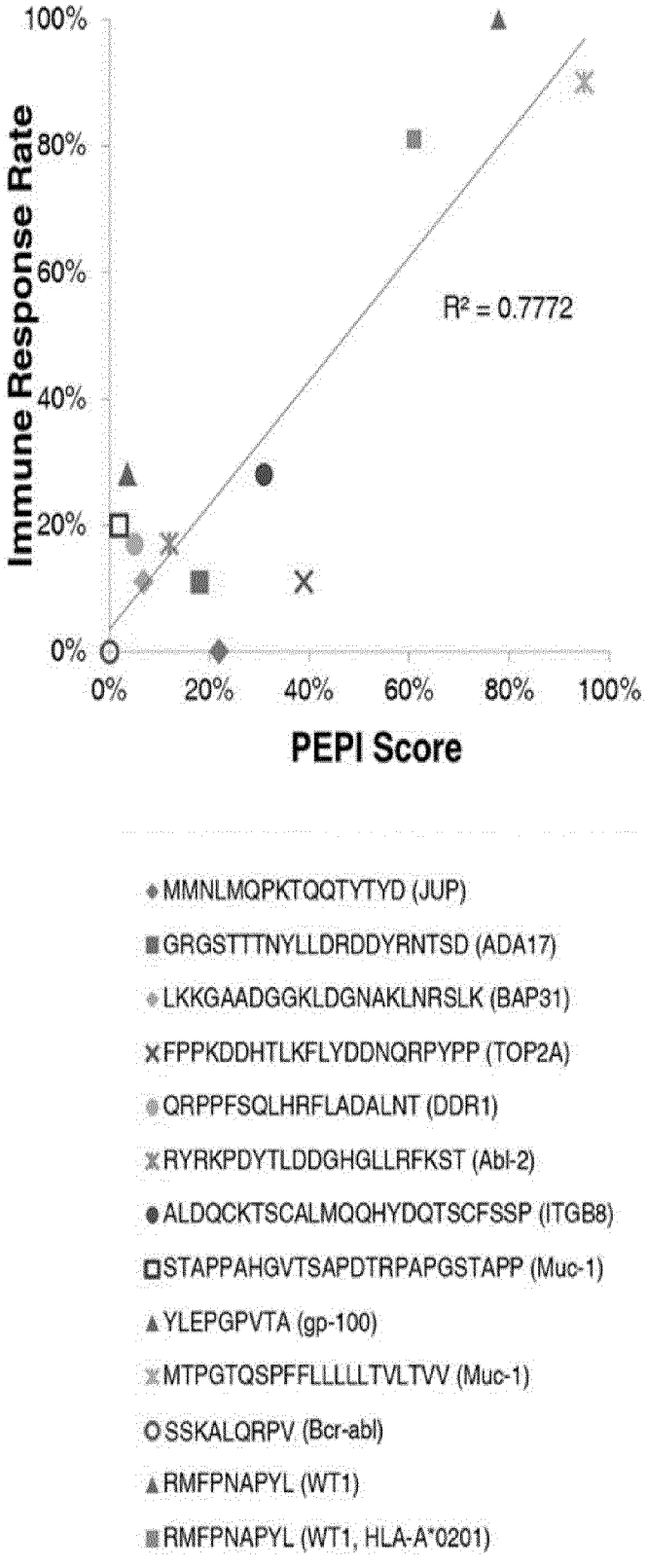
100%
80%
60%
40%
20%
0%
Immune Response Rate
R² = 0.7772
0%
20%
40%
60%
80%
100%
PEPI Score
MMNLMQPKTQQTYTYD (JUP)
GRGSTTTNYLLDRDDYRNTSD (ADA17)
LKKGAADGGKLDGNAKLNRSLK (BAP31)
FPPKDDHTLKFLYDDNQRPYPP (TOP2A)
QRPPFSQLHRFLADALNT (DDR1)
RYRKPDYTLDDGHGLLRFKST (Abl-2)
ALDQCKTSCALMQQHYDQTSCFSSP (ITGB8)
STAPPAHGVTSAPDTRPAPGSTAPP (Muc-1)
YLEPGPVTA (gp-100)
MTPGTQSPFFLLLLLTVLTVV (Muc-1)
SSKALQRPV (Bcr-abl)
RMFPNAPYL (WT1)
RMFPNAPYL (WT1, HLA-A*0201)

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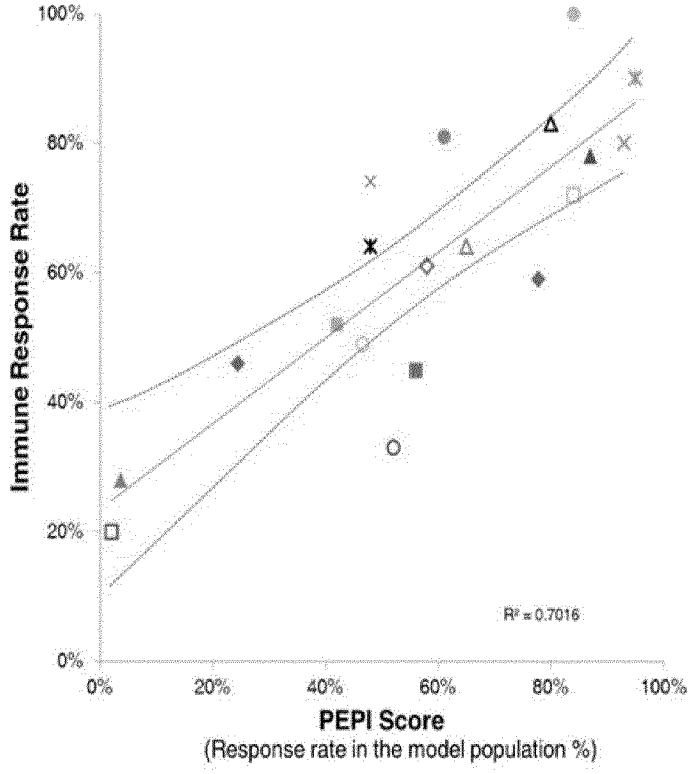
Figure 8



StimuVax (Merck)

gp100 vaccine (Sloan-Kettering Institute)

IMA901 (phase I, Immatics)

IMA901 (phase II, Immatics)

ICT107 (Cedars-Sinai Medical Center)

ProstVac (Bavarian Nordic)

Synchrotope TA2M (Mannkind Co.)

MELITAC 12.1 (Fred Hutchinson CRC)

WT1 vaccine (NCRC Hospital, Tokyo)

Iplilimumab (NY-ESO-1, MSKCC)

VGX-3100 (Inovio)

HIVIS-1 (Karolinska)

ImMucin (VaxilBio)

NY-ESO-1 OLP (Osaka University)

GVX301 (University Genoa)

WT1 vaccine (MSKCC)

WT1 vaccine (CBF)

DPX-0907 (ImmunoVaccine Inc.)

Melanoma peptide vaccine (University of Virginia)

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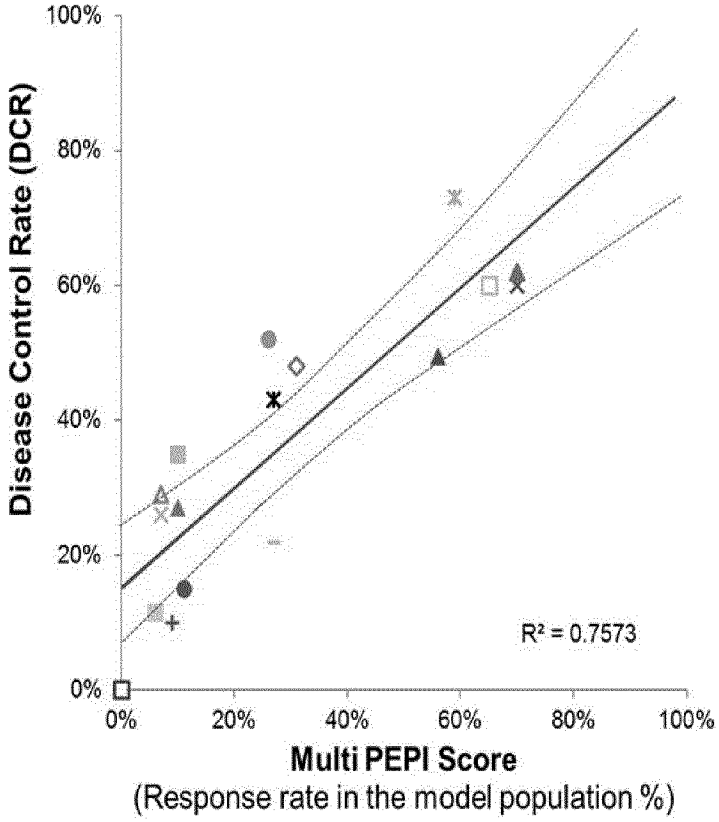
Figure 9



IMA901 (phase I, Immatics)

IMA901 (phase II, Immatics)

Iplilimumab (NY-ESO-1, MSKCC)

HPV-SLP (Leiden University)

HPV-SLP (Leiden University)

gp100 - 2 peptides (BMS)

ImMucin (VaxilBio)

StimuVax (Merck)

VGX-3100 (Inovio) [7]

TSPP (Siena University)

KIF20A-66 peptide (Chiba Tokushukai Hospital)

Peptide vaccine (Kumamoto University)

7-peptide cocktail vaccine (Kinki University)

GVX301 (University Genoa)

MAGE-A3 Trojan (Abramson Cancer Center)

PepCan (University of Arkansas)

Melanoma peptide vaccine (University of Virginia)

Figure 10

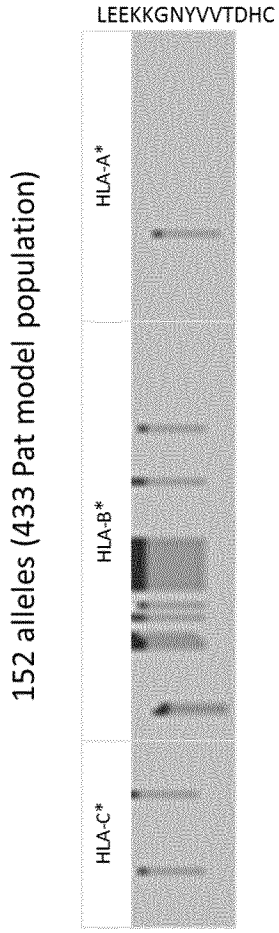

LEEKKGNYVVTDHC
152 alleles (433 Pat model population)
HLA-A*
HLA-B*
HLA-C*

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Figure 11

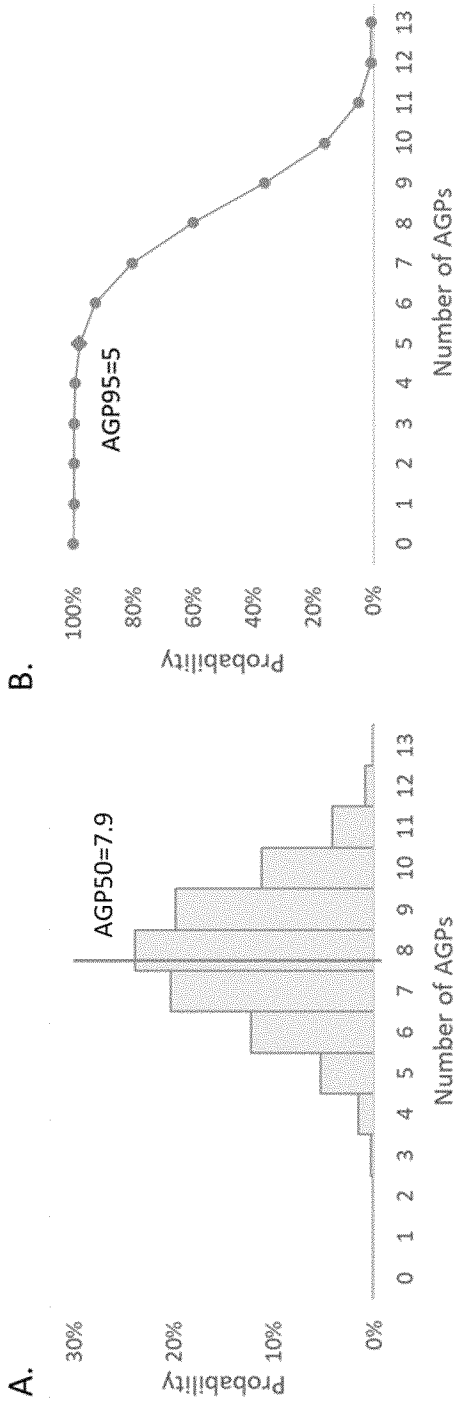

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Figure 12

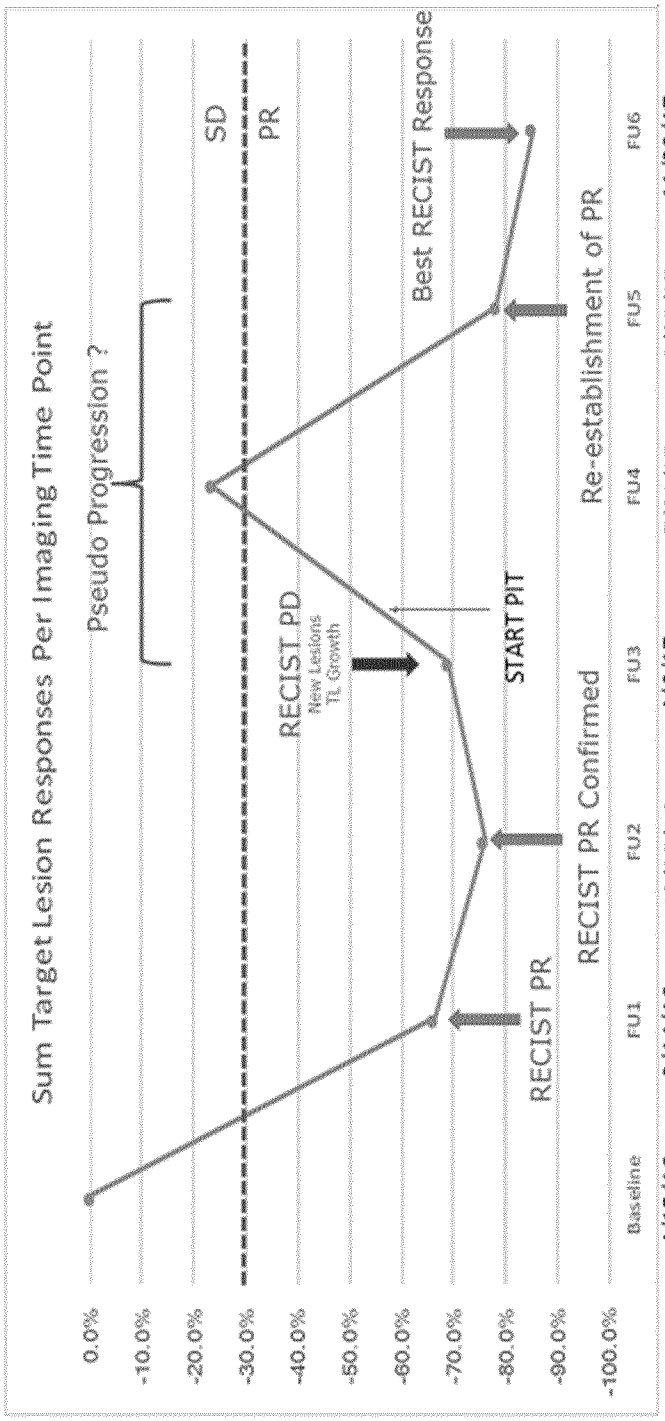

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Figure 13

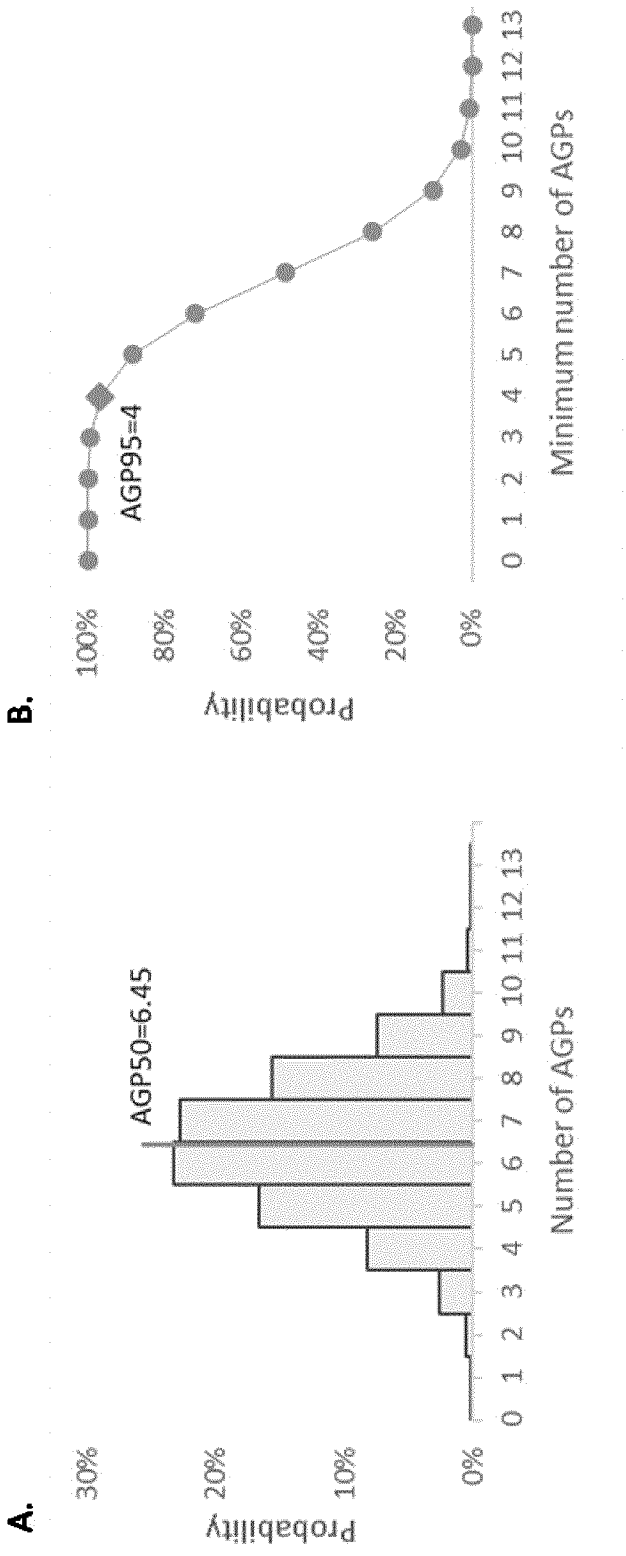

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Figure 14

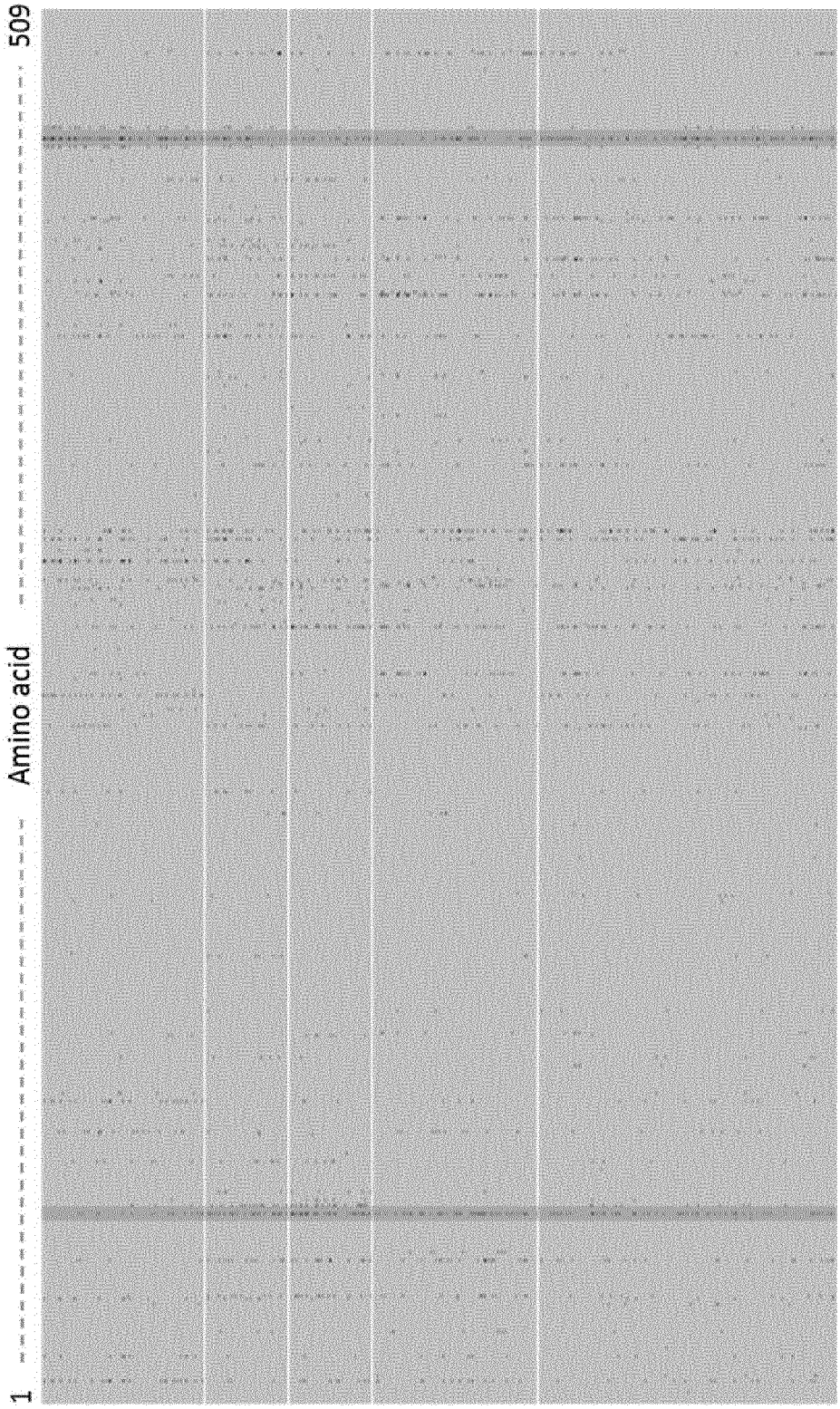

Figure 15

Antigens	Expression rate
Cancer testis antigens	Determined from 1053 tumor samples
AKAP-4	85%
BORIS	71%
SPAG9	88%
PRAME	55%
NY-SAR-35	48%
MAGE-A9	44%
NY-BR-1	47%
SURVIVIN	71%
MAGE-A11	59%
HOM-TES-85	47%

Conclusion

1. 99% of breast tumors express ≥3 antigens
2. No biopsy is needed

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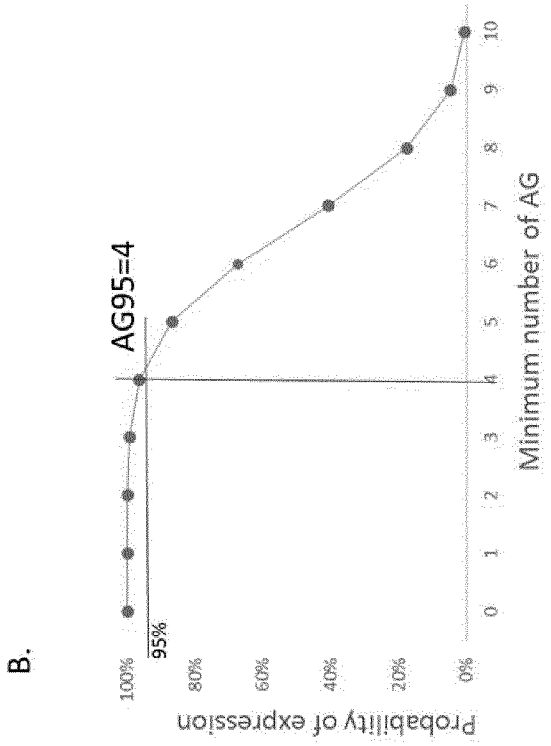
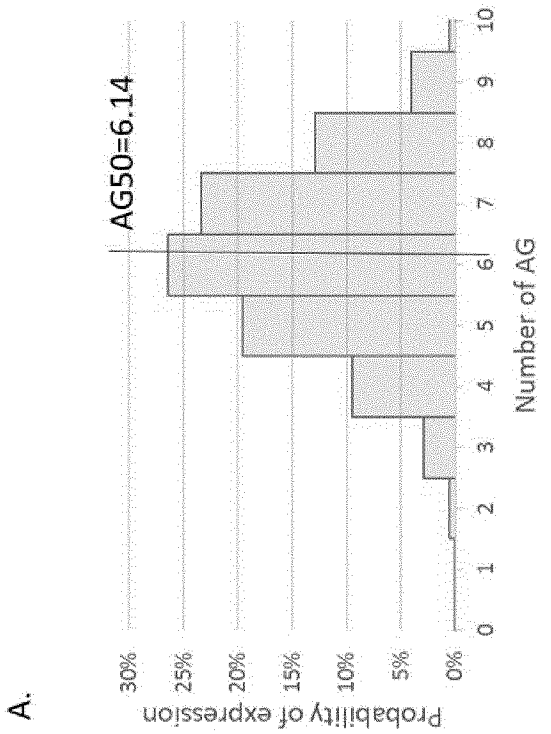
Figure 16





17/25
Figure 17

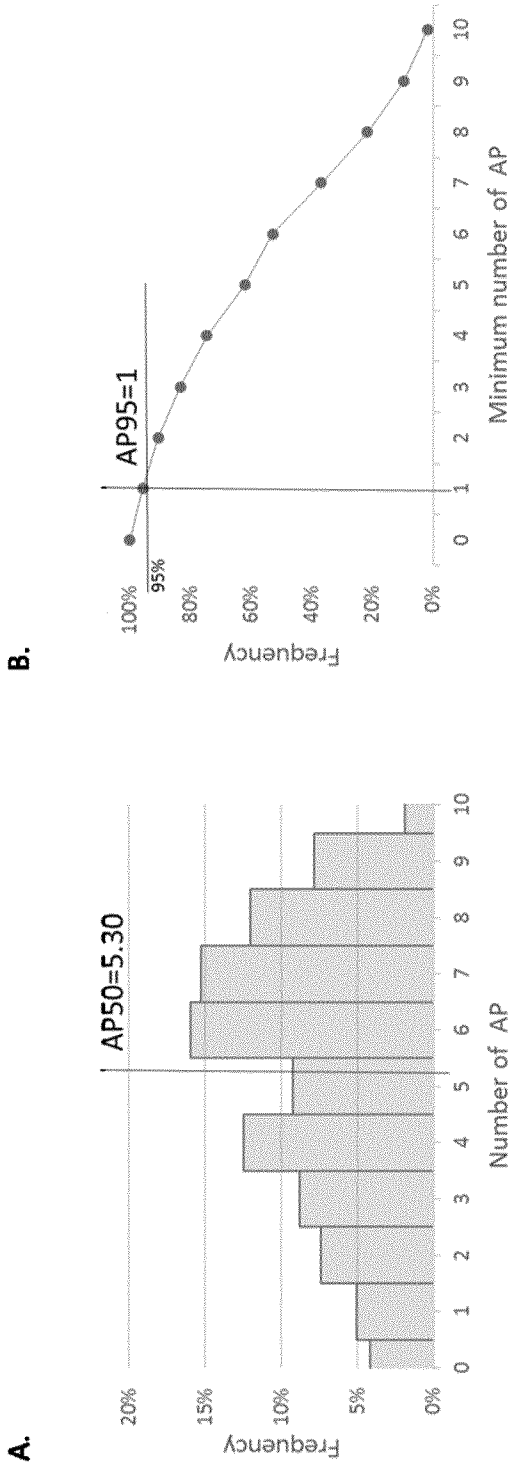


Figure 18

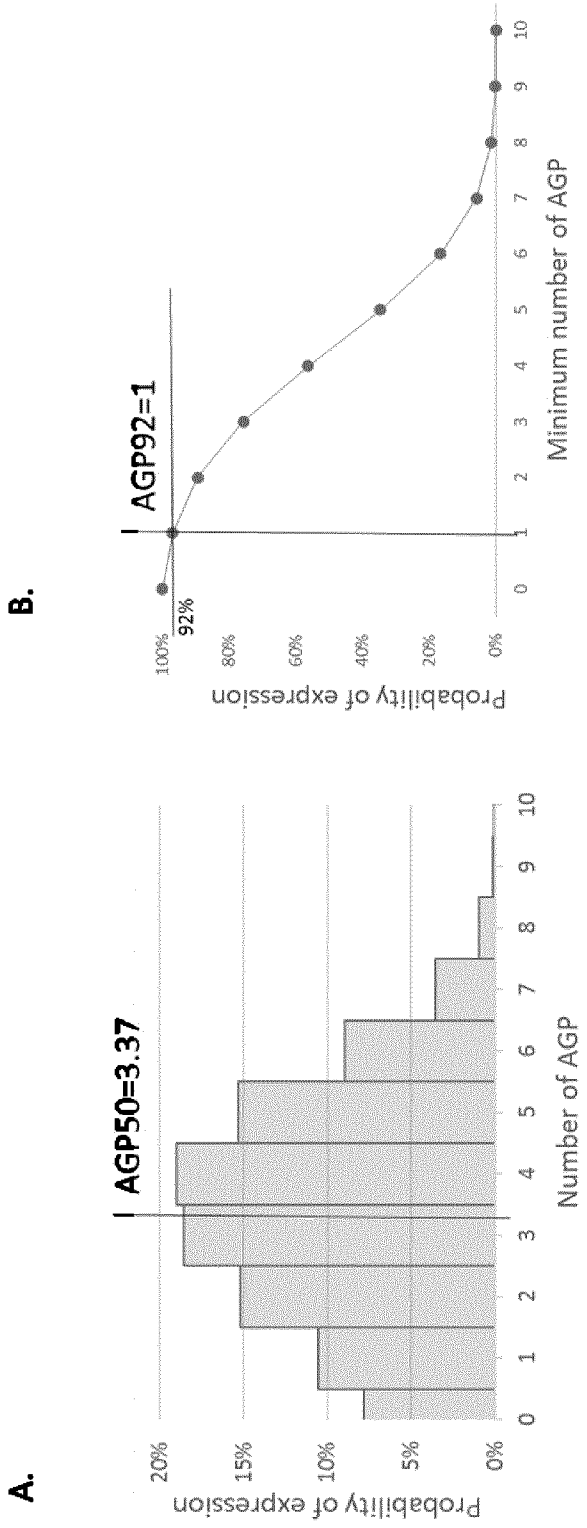

B.
AGP92=1
92%
100%
80%
60%
40%
20%
0%
Probability of expression
0
1
2
3
4
5
6
7
8
9
10
Minimum number of AGP
A.
AGP50=3.37
20%
15%
10%
5%
0%
Probability of expression
0
1
2
3
4
5
6
7
8
9
10
Number of AGP

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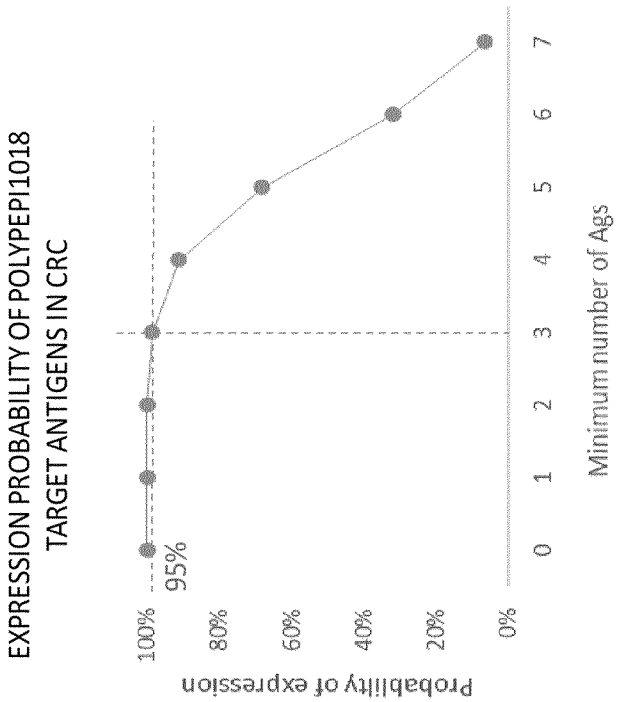
Figure 19

EXPRESSION RATES OF POLYPEPI1018
TARGET ANTIGENS IN CRC

TSP50	89.47%
EpCAM	88.35%
Survivin	87.28%
CAGE1	74.47%
SPAG9	74.36%
FBXO39	38.60%
MAGE-A8	43.75%



20/25
Figure 20

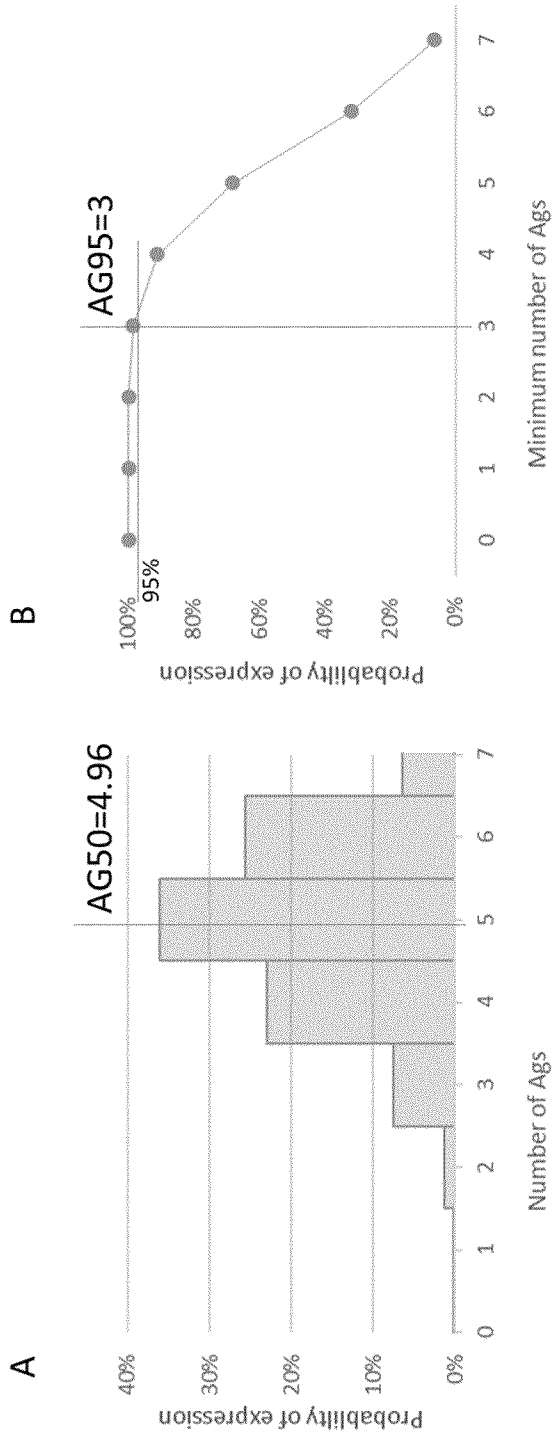


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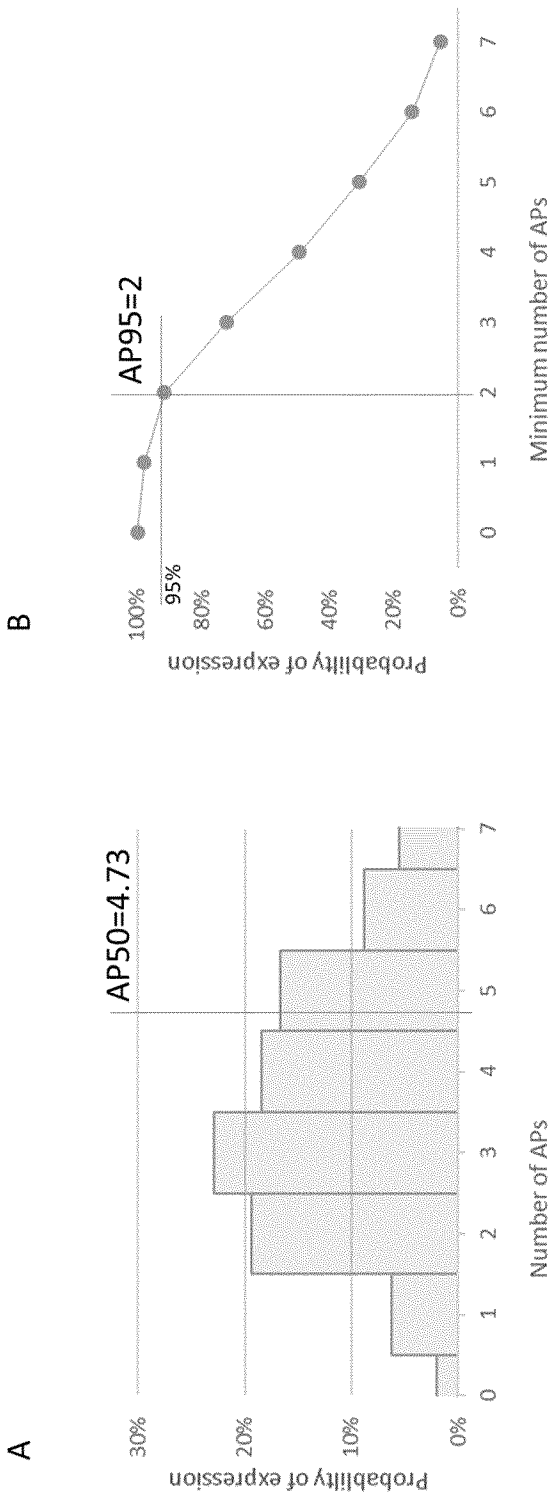
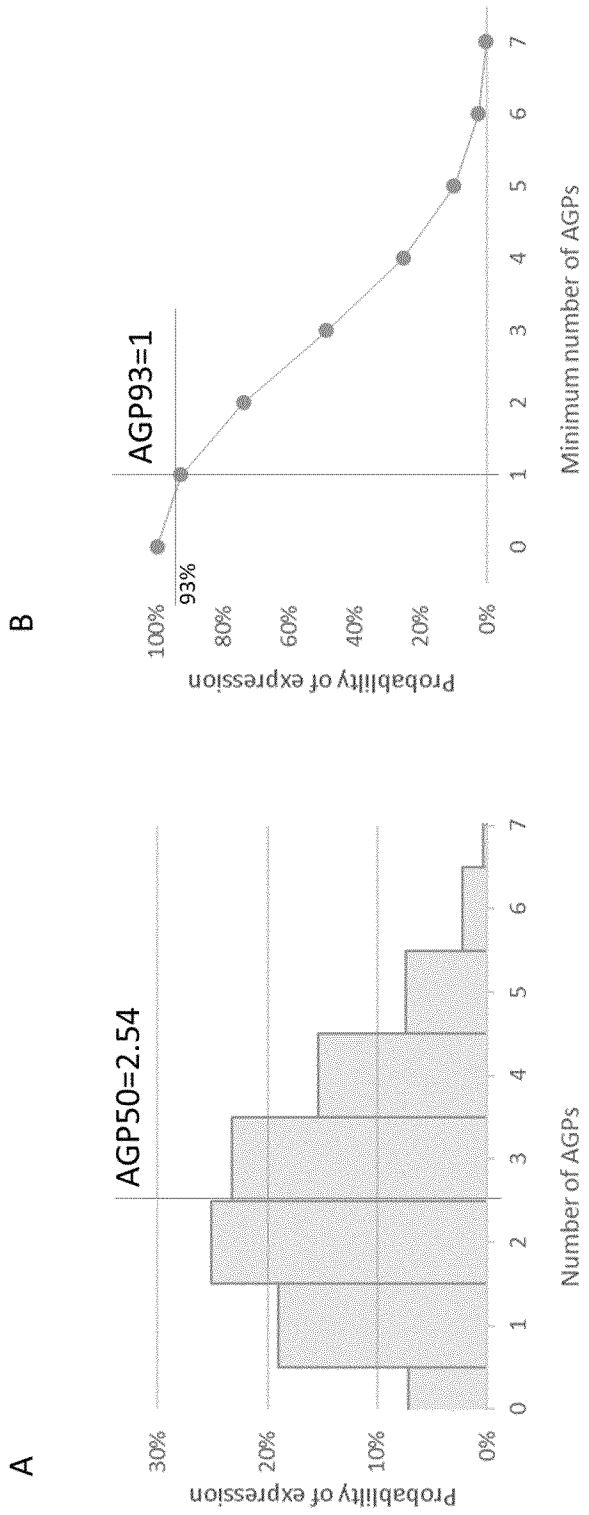
Figure 21



22/25
Figure 22



23/25
Figure 23

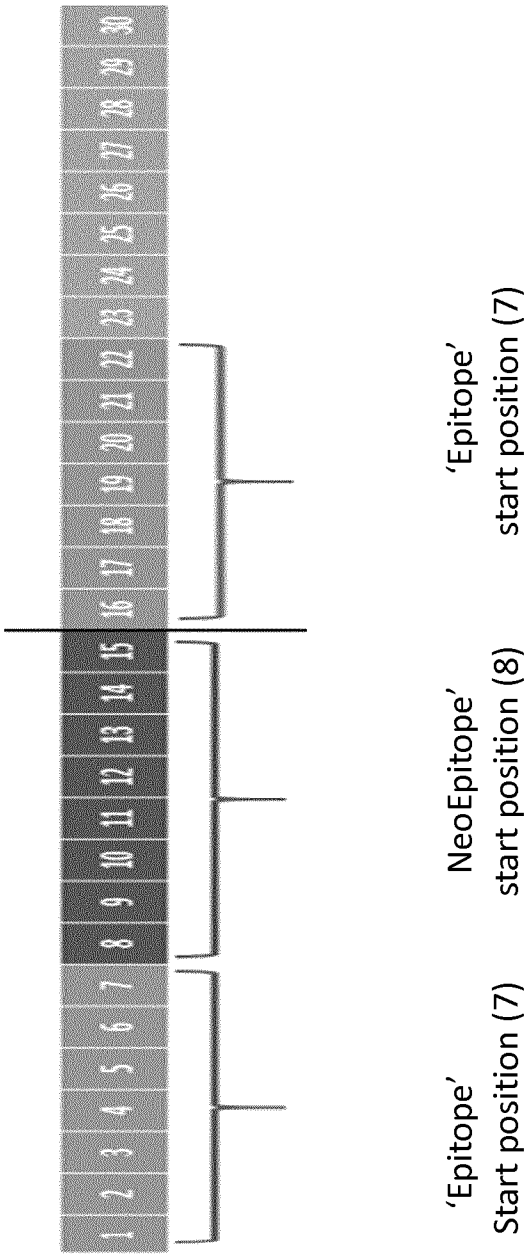
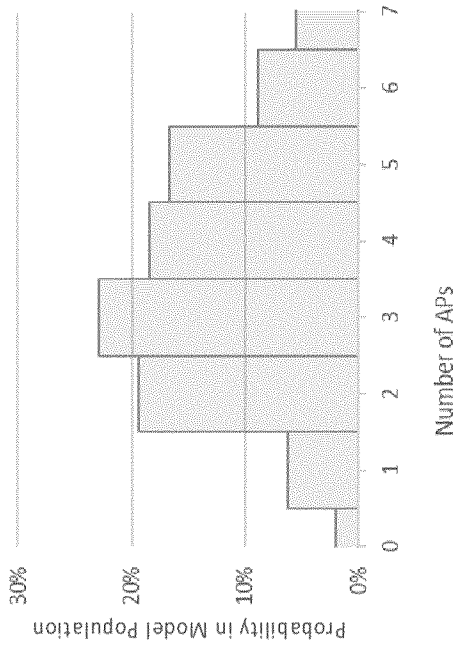


Figure 24


30%
20%
10%
0%
Probability in Model Population
0
1
2
3
4
5
6
7
Number of APs

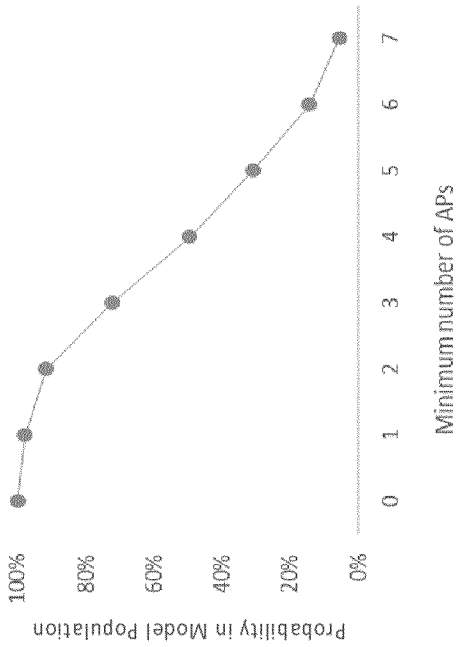
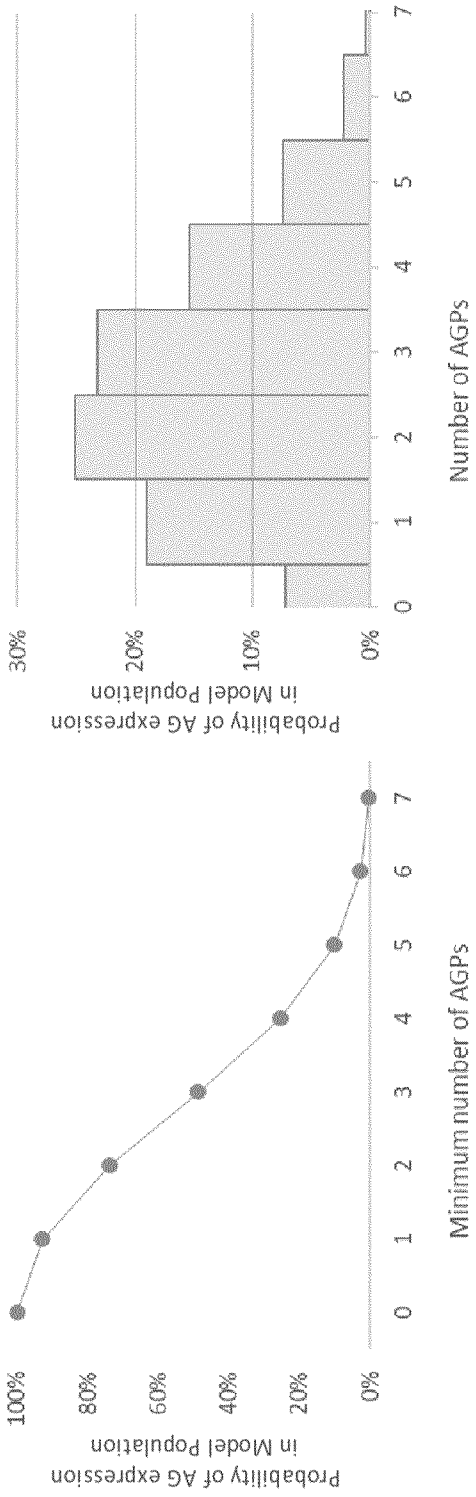

100%
80%
60%
40%
20%
0%
Probability in Model Population
0
1
2
3
4
5
6
7
Minimum number of APs

Figure 25


Probability of AG expression in Model Population
30%
20%
10%
0%
0
1
2
3
4
5
6
7
Number of AGPs
Probability of AG expression in Model Population
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
6
7
Minimum number of AGPs

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/055232

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/50 G01N33/569 A61K39/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SINGH SATARUDRA PRAKASH ET AL: "Major histocompatibility complex linked databases and prediction tools for designing vaccines", HUMAN IMMUNOLOGY, NEW YORK, NY, US, vol. 77, no. 3, 14 November 2015 (2015-11-14), pages 295-306, XP029497258, ISSN: 0198-8859, DOI: 10.1016/J.HUMIMM.2015.11.012	31,32
Y	page 296, right-hand column, paragraph 6 page 298, right-hand column, last paragraph - page 299, left-hand column, paragraph 1 page 302, left-hand column, paragraph 1 - page 304, right-hand column, last paragraph	1-6

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2018	09/05/2018

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMADA AKIRA ET AL: "Phase I clinical study of a personalized peptide vaccination available for six different human leukocyte antigen (HLA-A2,-A3,-A11,-A24,-A31 and-A33)-positive patients with advanced cancer", EXPERIMENTAL AND THERAPEUTIC MEDICINE,, vol. 2, no. 1, 1 January 2011 (2011-01-01) , pages 109-117, XP002779456,	7-12, 16-30
Y	page 109, right-hand column, paragraph 3 - page 110, left-hand column, paragraph 1 page 110, left-hand column, last paragraph - right-hand column, paragraph 3 page 112, right-hand column, paragraph 2 - page 116, left-hand column, paragraph 1 page 116, left-hand column, last paragraph - right-hand column, last paragraph	1-6

X	US 2010/074925 A1 (CARMON LIOR [IL]) 25 March 2010 (2010-03-25) page 3, paragraph 0033 - page 4, paragraph 0055 page 5, paragraph 0061 - page 7, paragraph 110 page 8, paragraph 0130 - paragraph 0134; tables 1, 3	8-30

A	EP 2 042 600 A1 (COMMISSARIAT ENERGIE ATOMIQUE [FR]) 1 April 2009 (2009-04-01) page 3, paragraph 0009 - page 4, paragraph 0017 page 5, paragraph 0019 - page 6, paragraph 0034 page 6, paragraph 0039 - page 7, paragraph 0045	1-32

A	ROSA DANIELA SANTORO ET AL: "Multiple Approaches for Increasing the Immunogenicity of an Epitope-Based Anti-HIV Vaccine", AIDS RESEARCH AND HUMAN RETROVIRUSES,, vol. 31, no. 11, 1 November 2015 (2015-11-01), pages 1077-1088, XP002779457, abstract page 1078, right-hand column, paragraph 6 - page 1080, left-hand column, paragraph 3; table 2 page 1085, left-hand column, paragraph 4 - right-hand column, paragraph 2	1-32

	-/--	

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RAJASAGI MOHINI ET AL: "Systematic identification of personal tumor-specific neoantigens in chronic lymphocytic leukemia", BLOOD,, vol. 124, no. 3, 1 July 2014 (2014-07-01), pages 453-462, XP002779455, page 454, left-hand column, paragraphs 3, 5, 6 page 455, left-hand column, paragraph 2 - page 456, right-hand column, paragraph 2 page 457, right-hand column, paragraph 2 - page 458, left-hand column, paragraph 1 -----	1-32
A	EP 2 745 845 A1 (CT HOSPITALIER UNIVERSITAIRE DE BORDEAUX [FR]) 25 June 2014 (2014-06-25) page 3, paragraph 0011 - paragraph 0014 page 4, paragraph 0024 page 4, paragraph 0027 - paragraph 0028 page 5, paragraph 0039 - page 7, paragraph 0059; example -----	1-32

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/055232

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010074925 A1	25-03-2010	AU 2007298494 A1	27-03-2008
		CA 2665816 A1	27-03-2008
		EP 2089423 A1	19-08-2009
		US 2010074925 A1	25-03-2010
		US 2017072036 A1	16-03-2017
		WO 2008035350 A1	27-03-2008
EP 2042600 A1	01-04-2009	EP 2042600 A1	01-04-2009
		WO 2009040674 A2	02-04-2009
EP 2745845 A1	25-06-2014	EP 2745845 A1	25-06-2014
		WO 2014095998 A1	26-06-2014