

PERSONALISED 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 personalised or 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.

In one aspect, the disclosure refers to a method of identifying a fragment of a polypeptide as immunogenic for a specific human subject or predicting whether a polypeptide or a fragment of a polypeptide is immunogenic for a specific human subject, the method comprising the steps of

(i) determining whether the polypeptide comprises:

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

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

(ii) (I) identifying said sequence as a fragment of the polypeptide that is immunogenic for the subject; or

(II) predicting

A. that the polypeptide is immunogenic for the subject if the polypeptide comprises at least one sequence that meets the requirements of step (i); or

B. 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).

In another aspect, the disclosure refers to the use of a checkpoint inhibitor in the preparation of a medicament for treating cancer in a human subject in need thereof, wherein the

subject has been predicted to respond, or to be likely to respond, to administration of the checkpoint inhibitor by a method as described herein.

In another aspect, the disclosure refers to an *in vitro* or *in silico* method of designing or preparing a human subject-specific pharmaceutical composition or kit or panel of polypeptides for treatment of a specific human subject, the method comprising:

(i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by the method as disclosed herein;

(ii) selecting a first sequence of up to 50 consecutive amino acids of the polypeptide, which consecutive amino acids comprise the amino acid sequence of the fragment selected in step (i);

(iii) repeating steps (i) and (ii) to select a second amino acid sequence of up to 50 consecutive amino acids of the same or a different polypeptide to the first amino acid sequence;

(iv) optionally further repeating steps (i) and (ii) to select one or more additional amino acid sequences of up to 50 consecutive amino acids of the same or different polypeptides to the first and second amino acid sequences; and

(vi) designing or preparing a subject-specific pharmaceutical composition, kit or panel of polypeptides having as active ingredients one or more polypeptides that together have all of the amino acid sequences selected in the preceding steps, optionally wherein one or more or each sequence is flanked at the N and/or C terminus by additional amino acids that are not part of the sequence of the polypeptides.

In yet another aspect, the disclosure refers to use of a pharmaceutical composition, kit or panel of polypeptides in the manufacture of a medicament for treating cancer in a specific human subject, wherein the pharmaceutical composition, kit or panel has been designed or prepared for treatment of the subject according to the method as described in the disclosure, and wherein each of the fragments selected in a step as disclosed herein is a fragment of a different cancer-associated antigen, optionally wherein the medicament is for prophylactic use in the subject.

In yet another aspect, the disclosure refers to a method of designing or preparing a polypeptide for inducing an immune response in a specific human subject the method comprising selecting an amino acid sequence that 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 the subject, and designing or
5 preparing a polypeptide comprising the selected amino acid sequence; optionally wherein the method is (a) a method of designing or preparing a polypeptide for inducing a cytotoxic T cell response in a specific human subject, the method comprising selecting an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject,
10 and designing or preparing a polypeptide comprising the selected amino acid sequence; or

(b) a method of designing or preparing a polypeptide for inducing a helper T cell response, the method comprising selecting an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject, and designing or preparing a polypeptide comprising the selected amino acid sequence.

In some embodiments the methods of the disclosure comprise the step of determining or obtaining the HLA class I genotype and/or the HLA class II genotype of the specific human subject.

A specific polypeptide antigen may comprise more than one fragment that is a T cell epitope capable of binding to multiple HLA of a specific individual. The combined group of all such fragments characterize the individual's antigen specific T cell response set, wherein the amino acid sequence of each fragment characterizes the specificity of each activated T cell clone.

5 Accordingly in some cases the method is repeated until all of the fragments of the polypeptide that are a T cell epitope capable of binding to at least two HLA class I and/or at least two HLA class II of the subject have been identified. This method characterises the immune response of the subject to the polypeptide.

10 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 by any of the methods above or comprising a fragment of a polypeptide that has been identified or selected by any of the methods 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.

15 The fragments of polypeptide that are determined to be immunogenic for a specific human subject in accordance with the methods above can be used to prepare human subject-specific immunogenic compositions.

20 Accordingly in a further example, the disclosure provides methods of designing or preparing a human subject-specific pharmaceutical composition or kit or panel of polypeptides for use in a method of treatment of a specific human subject, the methods comprising:

- (i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by the method above;
- (ii) if the fragment selected in step (i) is an HLA class I-binding epitope, optionally selecting a longer fragment of the polypeptide, which longer fragment
 - 25 a. comprises the fragment selected in step (i); and

- b. is a T cell epitope capable of binding at least three or to the most possible HLA class II molecules of the subject;
- (iii) selecting a first sequence of up to 50 consecutive amino acids of the polypeptide, which consecutive amino acids comprise the amino acid sequence of the fragment selected in step (i) or the longer fragment selected in step (ii);
- (iv) repeating steps (i) to (iii) to select a second amino acid sequence of up to 50 consecutive amino acids of the same or a different polypeptide to the first amino acid sequence;
- (v) optionally further repeating steps (i) to (iii) to select one or more additional amino acid sequences of up to 50 consecutive amino acids of the same or different polypeptides to the first and second amino acid sequences; and
- (vi) designing or preparing a subject-specific pharmaceutical composition, kit or panel of polypeptides having as active ingredients one or more polypeptides that together have all of the amino acid sequences selected in the preceding steps, optionally wherein one or more or each sequence is flanked at the N and/or C terminus by additional amino acids that are not part of the sequence of the polypeptides.

In some cases each peptide either consists of one of the selected amino acid sequences, or consists of two or more of the amino acid sequences arranged end to end or overlapping in a single peptide.

The disclosure further provides a human subject-specific pharmaceutical composition, kit or panel of polypeptides for use in a method of treatment of a specific human subject in need thereof, the composition, kit or panel comprising 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 a T cell epitope capable of binding to at least two HLA class I molecules and/or at least two HLA class II molecules of the subject, wherein the amino acid sequence of the 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 further provides a human subject-specific pharmaceutical composition, kit or panel of polypeptides for use in a method of treatment of a specific human subject in need thereof, the composition or kit comprising as an active ingredient a polypeptide comprising a first region and a second region and optionally one of more additional regions, wherein each region comprises an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules and/or at least two HLA class II molecules of the subject, wherein the amino acid sequence of 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 further provides a method of designing or preparing a polypeptide for inducing an immune response in a specific human subject the method comprising selecting an amino acid sequence that 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 the subject, and designing or preparing a polypeptide comprising the selected amino acid sequence.

In further examples, the disclosure provides

- a method of inducing an immune response or a method of treatment comprising administering to a human subject in need thereof a human subject-specific pharmaceutical composition, or the polypeptides a kit or panel as described above, wherein the composition, kit or panel of polypeptides is specific for the subject;
- a human subject-specific immunogenic composition, kit or panel as described above for use in a method of inducing an immune response or a method of treatment of the specific human subject; and
- use of a human subject-specific pharmaceutical composition or the polypeptides of a kit or panel as described above in the manufacture of a medicament, wherein the medicament is for inducing an immune response in or treating the specific subject.

In a further example the disclosure provides a system comprising

(a) a storage module configured to store data comprising the class I and/or class II HLA genotype of a subject and the amino acid sequence of one or more test polypeptides; and

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

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 polypeptides of the pharmaceutical composition or kit.

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 examples 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

The IPI-responder HLA Test. Overall Survival (OS) of melanoma patients treated with Ipilimumab. Data of 4 independent clinical trials: HLA responders (black line) and HLA non responders (gray line). Statistical analysis: Cox Proportional Hazards Survival Regression. A: Trial 1: 18 HLA responders and 30 HLA non responders; B: Trial 2: 24 HLA responders and 20 HLA non responders; C: Trial 3: 6 HLA responders and 11 HLA non responders; D: Trial 4: 13 HLA responders and 38 HLA non responders

Fig. 11

Multiple HLA binding peptides in mutational neoantigens. A: Correlation of mutational load, neoantigen load (neoantigens are neoepitopes according to van Allen) and B: Correlation of PEPI3+ load and clinical benefit (min-Q1-median-Q3-max).

Fig. 12

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

Fig. 13

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. 14

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. 15

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 16

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

Description of the Sequences

SEQ ID NOs 1-13 set forth the additional peptide sequences described in Table 17.

SEQ ID NOs: 14-26 set forth personalised vaccine peptides designed for patient XYZ described in Table 26.

SEQ ID NOs: 27-38 set forth personalised vaccine peptides designed for patient ABC described in Table 29.

SEQ ID NOs: 39-86 set forth further 9 mer T cell epitopes described in Table 33.

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. In some embodiments, the HLA genotype of an individual is obtained or determined by assaying a biological sample from the individual. The biological sample typically contains subject DNA. The biological sample may be, for example, a blood, serum, plasma, saliva, urine, expiration, cell or tissue sample. In some embodiments the biological sample is a saliva sample. In some embodiments the biological sample is a buccal swab sample. 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. In some embodiments, the HLA genotype is determined using sequence specific primer (SSP) technologies. In some embodiments, the HLA genotype is determined using sequence specific oligonucleotide (SSO) technologies. In some embodiments, the HLA genotype is determined using sequence based typing (SBT) technologies. In some embodiments, the HLA genotype is determined using next generation sequencing. 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 disclosed herein.

“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 specific human subject or identifying a fragment of a polypeptide as immunogenic for a specific human subject, 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, Tübingen 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, Tübingen Univ.	http://abi.inf.uni-tuebingen.de/Services/SVMHC/
SYFPEITHI, Biomedical Informatics, Heidelberg	http://www.syfpeithi.de/bin/MHCServer.dll/EpitopePrediction.htm
ETK EPITOOLKIT, Tübingen 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 invention comprise 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 specific human subject.

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 specific human subject. 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 specific 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 least four HLA class II of a specific 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 specific human subject.

In some cases, the disclosure 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 specific 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 at 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 HLA class II molecules of the subject.

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

Described herein are methods of predicting whether a polypeptide is immunogenic for a specific human subject and of identifying a fragment of a polypeptide as immunogenic for a specific human subject. 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
5 further described below.

The polypeptide or antigen may be expressed in the cells or specifically in diseased cells of the subject (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
10 may be present in a sample taken from the specific human subject. 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
15 sample obtained from the subject. 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
20 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
25 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. For example the subpopulation 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.

As provided herein the identification of mutational epitopes (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 polynucleotide or cell encoding one or more active ingredient polypeptides.

5 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
10 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.

15 Non-limiting examples of suitable polypeptides include those listed in one or more of Tables 2 to 7.

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
20 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 Q8WXT7.1	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*	CTCF1 Q8NI51.1*	CTDSP2 O14595.1	CTGF P29279.1
CTLA4 P16410.1	CTNNA2 P26232.1*	CTNNB1 P35222.1	CTNND1 O60716.1
CTSH P09668.1	CTSP1 AORZH4.1*	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	Q00888.1	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	Q8NOW7.1*
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		GAGE12F	P0CL80.1	GAGE12G	P0CL81.1	GAGE12H	A6NDE8.1
A1L429.1							
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	GNPMB	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 Q96R80.1	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	MCT5 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	MF 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 POC5K6.1*	NAE1 Q13564.1	Napsin-A O96009.1
NAT6 Q93015.1	NBAS A2RRP1.1	NBPFI2 Q5TAG4.1	NCOA4 Q13772.1
NDC80 O14777.1	NDUFC2 O95298.1	Nectin-4 Q96NY8.1	NEK2 P15955.1
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 Q8NOW4.1	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 Q9BWW7.1
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	Q9PIW9.1	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	Q9HBJO.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*
POTEG	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	PTFN20A	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	A6NKB9.1
RB1	P06400.1	RBL2	Q08999.1	RBM46	Q8TBY0.1*	RBP4	P02753.1
RCAS1	O00559.1	RCVRN	P35243.1	RECL4	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
RS1D1	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	TAT1	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	Q9HOM0.1	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	P9WPU1.1	P9WPU7.1	P9WPU3.1	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	Q5NFI1.1	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	Q5NHS1.1	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	Q5NFI7.1	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	P9WPK3.1	P9WHI1.1	P9WHV3.1	Q5NIA7.1	P9WG27.1	P9WTF3.1
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	P9WTH1.1	P9WIG1.1	P9WIG3.1	P9WIF5.1	P9WIF1.1	P9WIE7.1
P9WHW9.1	P9WI41.1	P9WT39.1	P9WT37.1	P9WI25.1	Q11031.1	P9WI47.1	P9WT23.1
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	Q6MXY2.1
Q50703.1	P9WHX3.1	P96221.1	Q7D589.1	P9WMA3.1	P9WKW1.1	P9WKS9.1	P9WM29.1
P9WGC1.1	P9WLZ5.1	P9WLZ3.1	P9WLX1.1	P9WLX9.1	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	P9WFF9.1	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	Q4WV16.1
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	Q4WT37.1	Q4WNI1.1
P29717.1	P46589.1	Q59W04.1	Q59RK9.1	B8MY56.1	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	B8NH4.1	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	Q4WTK9.1
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	Q4XIN0.1	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	B8NM2.1	Q4WEP7.1	Q4WXJ0.1	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	B8NXY0.1	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	Q5AET2.1	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	Q8NJV1.1	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	Q4WGS8.1
Q59KY8.1	Q9B8D5.1	O74261.1	P53709.1	B8NDE2.1	Q4WQZ5.1	Q4WFW2.1	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
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Q5A8N2.1	Q5AT22.1	Q59P11.1	Q59S63.1	B8MZ6.1	Q4WT66.1	Q4WYS7.1	Q4WL88.1
P40953.1	Q5A950.1	Q5ADN8.1	Q5A0Y2.1	B8NM67.1	Q4WY57.1	Q4WY08.1	Q4WGV9.1
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P10613.1	Q59UH7.1	Q5A7R7.1	Q59W52.1	B8NXJ2.1	Q4W946.1	Q4X1D2.1	Q4WKV8.1
Q5A5Q6.1	Q5ATX8.1	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	Q4WFX4.1	Q4WKB2.1
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P39827.1	Q59Z51.1	Q5ATA4.1	Q59XM0.1	B8MXP5.1	Q4WYU4.1	Q4WZJ0.1	Q9P8P4.1
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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
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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
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Q5AD05.1	Q5ABU8.1	Q5A310.1	Q59KG2.1	B8N6V7.1	Q4WZ61.1	Q4WXE9.1	Q4WMU5.1
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O13289.1	Q5AD67.1	Q5A7M3.1	Q5A7S5.1	B8NL00.1	Q4WUE0.1	Q4WAX1.1	Q4WHF8.1
P43063.1	Q59LV5.1	Q59QC4.1	O42817.1	B8NSP6.1	Q4WHP6.1	Q4WY16.1	Q4WV23.1
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Q59YH3.1	Q59ST8.1	Q5AKW3.1	Q59P44.1	B8NP78.1	Q4WTN9.1	Q4WBL2.1	Q6MY48.1
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G1UB63.1	Q5AED6.1	Q59X40.1	Q5A455.1	B8NJL4.1	Q6MYX3.1	Q4W9B9.1	Q4WNC1.1
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Q5A4X5.1	Q5A2W2.1	Q5A2A2.1	Q5ADP6.1	B8N7Z6.1	Q4WJ21.1	Q4WIT3.1	Q4WP96.1
Q5A4E3.1	Q5A4E2.1	Q5A044.1	Q5AK62.1	B8NGU1.1	Q4WPQ8.1	Q4WJA1.1	Q4WNS4.1
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P52496.1	Q59S50.1	Q5ANP2.1	Q59WD5.1	Q00049.1	P0C955.1	Q4X0Z7.1	Q4WVF4.1
Q9HEW1.1	Q5AD78.1	Q59933.1	Q5ABA2.1	B8NDP1.1	Q4WRH9.1	Q4WMS3.1	Q4WP02.1
Q5A6B6.1	Q5AMM4.1	Q3MPQ4.1	Q5A861.1	B8NEM4.1	Q4WVD1.1	Q4WN42.1	Q4WWH6.1
Q5A1W9.1	Q5AAW3.1	Q59MP1.1	Q5AH87.1	Q9P8Z9.1	Q4WID6.1	Q4WJH6.1	Q4WVE5.1
P30418.1	Q59MG1.1	Q59MB6.1	P33181.1	B8MZJ8.1	Q4WFX9.1	Q4WYS1.1	Q4WHP3.1
Q59SN6.1	Q5ACK7.1	Q5A216.1	Q59Q43.1	B8NX10.1	Q4WRE4.1	Q4WJ01.1	Q4WRE2.1
Q5A343.1	Q5A218.1	Q9UVL1.1	Q5A860.1	B8NV05.1	Q4WC60.1	Q4WGL2.1	Q4WYX0.1
Q5ABZ2.1	Q59SJ9.1	Q59YS7.1	Q59ZW9.1	B8NEI6.1	Q4WR18.1	Q4WP49.1	Q4WRB8.1
Q59MJ1.1	Q5AD49.1	Q5AGA0.1	A0A1D8PI78.1	B8MZT5.1	Q4WQY6.1	Q4WPE6.1	Q4WTI8.1
Q5AJ71.1	Q59NX9.1	Q5A687.1	Q59R24.1	B8NSJ0.1	Q4WXX4.1	Q4WWW9.1	Q4WQL0.1
O74201.1	Q5A119.1	Q59R28.1	Q5AHJ5.1	B8NDR8.1	Q4WTI96.1	Q4WKB5.1	Q4WDZ0.1
Q5AK54.1	Q59K07.1	Q5AJS6.1	P0C0X3.1	B8NDQ2.1	Q4WVH4.1	Q4WA38.1	Q4WA70.1
O93852.1	Q5AKA5.1	Q5AD59.1	Q59KL6.1	B8N9M0.1	A4D9R2.1	Q4WHL1.1	Q4WQ82.1
Q5AIR7.1	Q59QC2.1	Q5AG73.1	P43072.1	B8NLT6.1	P0C956.1	Q4X1X0.1	Q4WMX7.1
Q5A8K2.1	Q5AL45.1	Q5AND1.1	Q5AF54.1	B8N9X2.1	Q4WR22.1	Q4WRX2.1	Q4X0V2.1
Q8TGB2.1	P0CY19.1	Q59NG5.1	Q59W44.1	B8NM08.1	Q4WQY8.1	Q4WDH9.1	Q4WTI6.1
Q5A477.1	Q5AGC4.1	Q59N20.1	P48990.1	B8NSD4.1	Q4WJJ3.1	Q4WVG1.1	Q4WXA1.1
Q5AP95.1	Q5ALP1.1	Q59WJ5.1	Q59U67.1	B8N122.1	Q4X265.1	Q4WDE0.1	Q4WCV5.1
Q5AF03.1	Q5AK42.1	Q5AA50.1	Q5ANB7.1	B8NCF0.1	Q9UVX3.1	Q4WCX4.1	Q4W9M7.1
Q5AMQ4.1	Q5APG7.1	Q5A319.1	Q5A3Y5.1	B8NKS1.1	Q4WR19.1	Q4X122.1	Q4WQY9.1
Q5ANI6.1	Q59Y20.1	Q5AD27.1	Q59SI2.1	B8N3R8.1	Q4WTF3.1	Q4WZF1.1	Q4WX30.1
P78595.1	Q5ALL3.1	Q5AHI7.1	Q5APA2.1	B8NG55.1	Q4WLY1.1	Q4WMU1.1	Q4WUT7.1
Q874I4.1	Q5AAT0.1	Q5ANE3.1	P12461.1	B8NQ07.1	Q4WMU3.1	Q4WGB7.1	Q4WIQ2.1
Q9UWF6.1	Q59QD6.1	Q59S06.1	Q59TN1.1	B8N513.1	Q4WQG5.1	A4DA73.1	Q4X0Z2.1
Q9UW12.1	Q5AML1.1	P87185.1	Q5A416.1	B8N4F5.1	Q4WPE9.1	Q4WD81.1	Q4WQZ0.1
Q5AAL9.1	Q5ACM9.1	Q5AM50.1	O43133.1	B8NT06.1	Q4WAZ4.1	Q4WHG0.1	Q4WE58.1
Q5AD56.1	Q59Z14.1	Q9B8C8.1	Q59MI8.1	B8NH72.1	Q4WLN7.1	Q4WAJ6.1	Q4WJR4.1
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	Q4WT37.1	Q4WXT2.1
Q5AP52.1	Q5A1U8.1	Q59VX9.1	Q59NW5.1	B8NXP1.1	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	Q4X1T8.1

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	Q42716.1	Q4WVU5.1	Q4WXV2.1	Q4WQJ2.1
P0CY35.1	Q5AJ82.1	Q5AGW8.1	Q5ADL8.1	Q9UW95.1	Q4WLM7.1	Q4X0Z3.1	Q4WK56.1
Q5AAU5.1	Q5ATA1.1	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	Q4WKG6.1	Q4WQV2.1	Q4WX68.1
Q13426.1	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
Q59FF9.1	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	Q4WSP6.1	Q4WVZ3.1	Q4WPZL3.1	Q4WZS3.1
Q74254.1	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	Q74711.1	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	Q4WVF6.1
Q5AJV5.1	A0A1D8PK89.1	Q5A1E1.1	Q59R32.1	Q4WR82.1	Q4WZC3.1	Q4WRU4.1	Q4WKD9.1
Q5A3Z6.1	Q59WB3.1	Q59L86.1	Q5A061.1	Q14434.1	Q4WYX7.1	Q4WGS4.1	Q4WP10.1
Q5A201.1	Q59ZC8.1	Q5AD23.1	Q59P50.1	Q4WMK0.1	Q4X0A5.1	Q4WP13.1	C5JZM2.1
Q93827.1	Q5A1L6.1	Q5A5U6.1	Q59WC6.1	Q4WPX2.1	Q4WUD3.1	Q4WJG5.1	P0DJ06.1
Q5AAI8.1	A0A1D8PN14.1	Q5ADQ7.1	Q5AI48.1	Q43099.1	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	Q42799.1	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	Q65002.1	P05814.1
P13916.1	Q9UAMS.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

Q04298.1	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
Q52QK5.1	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	A5HTI1.1
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_00165755 6._2	P18153.2	AAB58417.1	ABF18122.1	XP_00165346 2._1	XP_00165414 3._1
XP_00165429 1._1	ABF18258.1	XP_00165594 8._1	XP_00165595 4._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	Q7M4T5.1	P01502.1
P00630.3	ABF21077.1	ABF21078.1	Q08169.1	ACT25605.1	Q5BLY5.1	CAA26038.1	MEHB2
NP_00111971 5._1	NP_00103536 0._1	ABD51779.1	NP_00101156 4._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
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AAQ10271.1	AAQ10268.1	AAQ08190.1	ABP58632.1	ABP58633.1	ABP58635.1	ABP58636.1	ABP58637.1
AAI92578.1	AAK88919.1	ACZ57582.1	E1U332.1	E3SU11.1	Q24170.1	Q24171.1	A4GFC0.1
A4GFC3.1	CAA73035.1	AAD05375.1	AAO33897.1	P80740.2	CAD21706.2	ABP58627.1	ABX26131.1
ABX26132.1	ABX26134.1	ABX26138.1	ABX26139.1	ABX26140.1	ABX26141.1	ABX26143.1	ABX26145.1
ABX26147.1	ABX54842.1	ABX54844.1	ABX54849.1	ABX54855.1	ABX54859.1	ABX54862.1	ABX54864.1
ABX54866.1	ABX54869.1	ABX54876.1	ABX54877.1	AAB66909.1	P81430.2	AAF31152.1	AAF31151.1
AAK58515.1	2JON A	BAE54432.1	Q25632.1	BAJ07603.1	P86431.1	P86432.1	BAF95206.1
AFV53352.1	AAG42806.1	AAG42802.1	Q948T6.2	AAA86533.1	AAF72991.1	BAB71741.1	Q40638.2
BAD13150.1	BAC20657.1	BAA01998.1	BAA01996.1	BAA07772.1	BAA07773.1	BAA07774.1	BAA07710.1
BAA07711.1	BAA07712.1	BAA07713.1	AAB99797.1	Q01882.2	Q01883.2	BAC19997.1	BAC20650.1
ADK39021.1	ACA96507.1	CBY17558.1	AAC38996.1	BAF47265.1	BAF47266.1	2008179A	CAA65123.1
CAA54587.1	CAT94601.1	CAA59370.1	CAA65122.1	P55958.1	Q9T0M8.1	Q9XG85.1	CCP19647.1
CAP05019.1	Q7M1E8	AAB36008.1	AAB36009.1	AAB36010.1	AAB36011.1	AAB36012.1	AAB46820.1
AAB46819.1	AKF12278.1	CBM42667.1	CBM42666.1	CBM42665.1	CBM42664.1	CBM42663.1	CBM42662.1
CBM42661.1	CBM42660.1	ACA23876.1	AAX37288.1	AAO15713.1	C7E3T4.1	ADV17342.1	ADV17343.1
AAK11194.1	AAF71379.1	AAG44693.2	AAF23726.1	AAM33821.1	AAB34785.1	ADK27483.1	AAD25995.1
AAG44480.1	Q92260.1	AAK51201.1	AAR17475.1	AAD42074.1	ABB89950.1	ABM60783.1	AAD25926.1
AEX34122.1	AAG44478.1	AKH04310.1	AKH04311.1	AAX33729.1	AEV23867.1	AAD19606.1	CAB38086.1
ACS14052.1	AAC34736.1	AAC34737.1	AAB82404.1	AAC34312.1	AAD13533.1	AAK13554.1	ADB92492.1
AAX33734.1	AAX33727.1	ADR82198.1	AAB09632.1	AAB62731.1	AAB63595.1	Q25641.1	ADB92493.1
ADD17628.1	AAX33728.1	3EBW A	ACJ37391.1	AAX33730.1	AAT77152.1	ACA00204.1	AAL86701.1
AAG08988.1	CAB01591.1	AAB27445.1	Q41260.1	P56164.1	P56165.1	P56166.1	P56167.1
ADC80502.1	ADC80503.1	CAA55390.1	CAA81613.1	1N10 A	CAG24374.1	2118271A	AAN32987.1
CAA70609.1	ABG81289.1	ABG81290.1	ABG81291.1	ABG81292.1	ABG81293.1	ABG81294.1	ABG81295.1
CAA70608.1	CAA54686.1	CAB42886.1	CAA53529.1	CAD54670.2	CAF32567.2	CAF32566.2	CAQ55938.1
CAQ55939.1	CAQ55940.1	CAQ55941.1	3TSH A	CAD54671.2	CAA52753.1	S32101	S38584
Q7M1L8	2023228A	CAB05371.1	CAB05372.1	CAA50281.1	AAC16525.1	AAC16526.1	AAC16527.1
AAC16528.1	AAC25994.1	AAC25995.1	AAC25997.1	AAC25998.1	AAC25823.1	CAD38384.1	CAD38385.1
CAD38386.1	CAD38387.1	CAD38388.1	CAD38389.1	CAD38390.1	CAD38391.1	CAD38392.1	CAD38393.1
CAD38394.1	CAD38395.1	CAD38396.1	CAD38397.1	1L3P A	CAD87529.1	CAA81609.1	CCD28287.1
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	AA11261.1	AA11262.1	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	AA137321.1	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	ACT41244.1	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	AA177383.1	AA177384.1	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	ATL01319.1	ATL01318.1	ATL01316.1	ATL01317.1
ATL01320.1	ATL01321.1	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	CAA34285.1	AAA34286.1	AAA34287.1	Q22116	CAA59338.1
CAA59339.1	CAA59340.1	Q22108	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	ACT44002.1
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	IQNX A	P49370.1	CAI77218.1	2ATM A	ACA00159.1	AA19889.1
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	Q6QJN1.1	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
Q8NFOU.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	Q9D7D4.1	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	Q72460.1
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	Q86SQ0.1	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
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P18146.1	Q05BV3.1	Q6ZMW3.1	O95967.1	P15502.1	Q9BY07.1	P13804.1	Q6PJG2.1
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P14625.1	Q14511.1	Q6P2E9.1	B2RL7.1	O84591.1	Q9Z7A6.1	P03188.1	P04578.1

P14075.1	Q6SW67.1	Q92817.1	P12724.1	Q12929.1	P61916.1	P07099.1	P03211.1
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P02751.1	Q4ZHG4.1	P20930.1	P21333.1	P30043.1	O75955.1	Q14254.1	P49771.1
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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
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P20592.1	Q9BYX4.1	O14879.1	Q12905.1	Q12906.1	P42701.1	Q5TF58.1	Q9NZM3.1
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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 provides 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 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 specific 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, anaphylaxis
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	thrombocytopenia
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 inventors have discovered that 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.

Therefore, in some cases the disclosure provides 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 than 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 specific 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 PEPs, 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 effected 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 PEPs 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 PEPs in the active ingredient polypeptides; (ii) the presence of PEPs 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 at least 3 HLAs of a subject and induce T cell responses. PEPI3+ can be determined using the PEPI3+ Test in subjects whose complete 4-digit HLA genotype is known.

- 5 • **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).
- 10 • **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.
- 15 • **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).
- 20 • **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

25 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

30 population, where no subject has a PEPI from any vaccine antigen, the AGP50 will be 0. In general, the following statement is valid: $0 \leq \text{AGP50} \leq \text{AG50}$.

- **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 in e.g. the tumor and the presence of vaccine derived PEPs 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 treatment comprising 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 PEP3+ count (for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 or more PEP3+), a minimum 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 specific human subject.

Predicting an autoimmune or toxic immune response to a polypeptide antigen

The differences among HLAs may influence the probability of developing an autoimmune disease, condition or response. In some cases the method of the disclosure may be used to identify a polypeptide or a fragment of a polypeptide that is immunogenic and/or associated with an auto-immune disorder or response. In some cases, the method comprises determining whether a polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three, or at least four, or at least five HLA class I of a subject; or in other cases a sequence that is a T cell epitope capable of binding to at least four, or at least five, or at least six HLA class II of a subject; and identifying the polypeptide or said sequence as immunogenic or as being related to or associated with an auto-immune disorder or an auto-immune response in the subject.

The differences among HLAs may also 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, in some cases in accordance with the disclosure, the method is used to identify a toxic immunogenic region or fragment of a polypeptide or to identify 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.

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 administering 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 specific human 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 specific human subject or in a proportion of a human population using any one of the methods described herein. The polypeptide may be mutated to reduce the number of PEPs 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 administering to the subject such a mutated polypeptide.

Predicting the response of an individual to treatment with a checkpoint inhibitor

Typically some or all of the tumor specific T cell clones that are induced by a tumor are inactive or poorly functional in metastatic cancer patients. Inactive tumor specific T cells cannot kill the tumor cells. A fraction of these inactive T cells may be re-activated by checkpoint inhibitors (such as Ipilimumab), for example monoclonal antibodies that recognize checkpoint molecules (e.g. CTLA-4, PD-1, Lag-3, Tim-3, TIGIT, BTLA). According to the present disclosure, treating a subject with a checkpoint inhibitor will only be effective if or to the extent

to which expressed cancer-antigens can be adequately recognised by the HLA of the individual, i.e. if there are epitopes in cancer- or disease-associated antigens that are recognised by multiple, preferably at least three, HLA class I molecules of the subject. Therefore, in some cases, the methods of the disclosure may be used to identify one or more or the subset of T cell clones that may be reactivated by a checkpoint inhibitor or to predict likely responders to checkpoint inhibitor (immuno)therapies.

Accordingly in some cases the disclosure provides a method of predicting whether a subject will respond to of cancer with a checkpoint inhibitor. In some cases the method comprises the step of identifying or selecting one or more polypeptides or polypeptide fragments that are associated with the disease or condition that is to be treated or that is associated with achieving an immune or clinical response to treatment with a checkpoint inhibitor. In some cases the polypeptide is a tumor-associated and/or mutational antigen. The polypeptide may be present in a sample obtained from the subject. The polypeptide may be one that is frequently (over-) expressed in a subject- and/or disease-matched population. The polypeptide may consist of or comprise a PEPI (or PEPI3+) identified in a subject that is known to have positively responded to a, or the, checkpoint inhibitor. The polypeptide may comprise or consist of an amino acid sequence that is stored or recorded in or retrieved from a database.

In some cases the method comprises determining whether the polypeptide(s) comprise a sequence that is a T cell epitope capable of binding to multiple HLA class I molecules of the subject. In some cases the presence of at least two, or at least three, or four or five or six or seven or eight different such amino acid sequences is determined, and/or the presence of such an amino acid sequence in at least two, or at least three, or four or five different target polypeptide antigens. In some cases the method comprises determining whether the polypeptide(s) comprise a sequence that is a T cell epitope capable of binding to at least two, or in some cases at least three or at least four HLA class II molecules of the subject. A response to treatment with the or a checkpoint inhibitor may be predicted if the above requirement(s) is met. No response or no clinical response may be predicted if the above requirement(s) is not met.

The disclosure also provides a method of identifying a fragment of a polypeptide or a T cell epitope in a polypeptide that may be targeted by the subject's immune response following treatment with a checkpoint inhibitor, or that will be targeted by T cells that are re-activated by treatment with a checkpoint inhibitor.

5 The method may further comprise selecting, recommending and/or administering a checkpoint inhibitor to a subject who is predicted to respond, or selecting, recommending and/or administering a different treatment to a subject that is predicted not to respond to a checkpoint inhibitor. In other cases the disclosure provides a method of treatment of a human subject in need thereof, the method comprising administering to the subject a checkpoint inhibitor, wherein the
10 subject has been predicted to respond to administration of a checkpoint inhibitor by the method described herein.

Checkpoint inhibitors include, but are not limited to, PD-1 inhibitors, PD-L1 inhibitors, Lag-3 inhibitors, Tim-3 inhibitors, TIGIT inhibitors, BTLA inhibitors and CTLA-4 inhibitors, for example. Co-stimulatory antibodies deliver positive signals through immune-regulatory receptors
15 including but not limited to ICOS, CD137, CD27 OX-40 and GITR. In one embodiment the checkpoint inhibitor is a CTLA-4 inhibitor.

Design and preparation of pharmaceutical compositions for an individual human subject

20 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 specific human subject. The disclosure also provides a human subject-specific drug, immunogenic composition, or pharmaceutical composition, kit or panel of peptides, methods of designing or preparing the same, compositions
25 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 the subject. The pharmaceutical composition, kit or panel of peptides has as active ingredients one or more polypeptides that

together comprising two or more T cell epitopes (PEPIs) capable of binding to multiple HLA class I or multiple HLA class II molecules of the subject that are immunogenic for the subject as described herein or that have been identified as immunogenic for the subject by a method described herein.

5 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 PEPIs. 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,
10 treat, or cure a disease of an individual, such as a cancer.

 Typically each PEPI is a fragment of a target polypeptide antigen and polypeptides that comprise one or more of the PEPIs 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
15 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 PEPI 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
20 herein, which consecutive amino acids comprise the amino acid sequence of the PEPI.

 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
25 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 PEPs 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 peptides may be screened, to avoid or eliminate 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 molecules of the subject. 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 multiple HLA-binding PEPs of the composition polypeptides may both target a single antigen (e.g. a polypeptide vaccine comprising two multiple HLA-binding PEPs 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 PEPs. The PEPs 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

specific subject 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.

5 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
10 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 PEPs in a single treatment (administration of
15 one or more pharmaceutical compositions that together comprise multiple PEPs), can be illustrated by the personalised vaccine polypeptides described in Examples 17 and 18 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 PEPs in only BAGE and MAGE A9, then the probability of having a mAGP
20 (multiple expressed antigens with PEPI) would be 11%. If patient XYZ were treated with a vaccine comprising only PEPs 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
25 two-PEPI treatments (probability mAGP for BAGE/MAGE + probability mAGP for MAGE A4 and MAGE A10). Patient XYZ's PIT vaccine described in Example 17 contains a further 9 PEPs, 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 18 contains a further 8 PEPIs, and thus, the probability of having a mAGP is over 99.93%.

Accordingly in some cases the PEPIs 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 the specific human subject. 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. Since mutational

neoantigens are subject specific, a composition that targets one or more neoantigen specific mutations is personalised with regard to both their specific disease and their specific HLA set.

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 may comprise identifying or selecting such a target polypeptide antigen. In some cases two or more or each of the immunogenic polypeptide fragments/PEPIs 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/PEPIs 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 the subject 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, 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 specific human 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, cyclophosphamide, bacillus Calmette-Guerin (BCG), corynebacterium parvum, levamisole, azimezone, isoprinosine, dinitrochlorobenzene (DNCB), keyhole limpet hemocyanins (KLH), Freund's adjuvant (complete and incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, peptides, 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 α , 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 PEPs 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 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
5 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
10 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
15 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
20 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-
25 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
5 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. Multiple pharmaceutical compositions of PEPs, manufactured for use in one regimen, may define a drug product.

10 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 skilled artisan will recognize that compositions of the disclosure may also be
15 administered in one, or more doses, as well as, by other routes of administration. For example, such other routes include, intracutaneously, intravenously, intravascularly, intraarterially, intraperitoneally, intrathecally, intratracheally, intracardially, intralobally, intramedullary, 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
20 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
25 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/checkpoint 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-sarcosine) and chlorambucil; anthracyclines; epothilones; nitrosoureas such as carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU) and streptozocin (streptozotocin); triazines 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 IFN α , 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, 5 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, 10 bleomycin, plicamycin (mithramycin) and mitomycin (mitomycin C), enzymes such as L-asparaginase, and biological response modifiers such as interferon alphas.

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 15 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 PEPs to an individual to elicit a T cell response to recognize and kill cells that display the one or more PEPs on their cell surface in conjunction with a class I HLA. In another 20 specific embodiment, immunotherapy comprises the administration of one or more PEPs 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 PEPs 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 PEPs presented by class II HLAs to an 25 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 PEPs 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 PEPs, 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.

5 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).

10 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
15 comprising the class I and/or class II HLA genotype of a subject and the amino acid sequence of one or more test polypeptides; and a computation module configured to identify and/or quantify amino acid sequences in the one or more test polypeptides that are capable of binding to multiple HLA of the subject. The system may be for obtaining data from at least one sample from at least one subject. The system may comprise a an HLA genotyping module for determining the class I
20 and/or class II HLA genotype of a subject. The storage module may be configured to store the data output from the genotyping module. The HLA genotyping module may receive a biological sample obtained from the subject and determines the subject's class I and/or class II HLA genotype. The sample typically contains subject DNA. The sample may be, for example, a blood, serum, plasma, saliva, urine, expiration, cell or tissue sample. The system may further
25 comprise an output module configured to display the sequence of one or more fragments of the one or more polypeptides that are predicted to be immunogenic for the subject, or any output prediction or treatment selection or recommendation described herein or the value of any pharmacodynamic biomarker described herein.

Further embodiments of the disclosure

1. A human subject-specific pharmaceutical composition for treatment of a disease or disorder in a specific human subject, comprising
 - 5 (a) at least two different polypeptides, each of the at least two different polypeptides being 10-50 amino acids in length and comprising a T cell epitope that binds at least three HLA class I molecules of the subject and/or at least three HLA class II molecules of the subject, and wherein the T cell epitope of each of the at least two polypeptides are different from each other; and
 - 10 (b) a pharmaceutically-acceptable adjuvant.
2. The human subject-specific pharmaceutical composition of item 1, 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.
3. The human subject-specific pharmaceutical composition of item 1, comprising 3-40 different polypeptides.
4. The human subject-specific pharmaceutical composition of item 1, 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.
- 20 5. The human subject-specific pharmaceutical composition of item 1, wherein the epitopes of the at least two different polypeptides are from a single antigen.
6. The human subject-specific pharmaceutical composition of item 1, wherein the epitopes of the at least two different polypeptides are from two or more different antigens.
7. The human subject-specific pharmaceutical composition of item 5, wherein the antigen is an antigen expressed by a cancer cell, a neoantigen expressed by a cancer cell, a cancer-
- 25

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.

- 5 8. The human subject-specific pharmaceutical composition of item 7, wherein the cancer cell is from the subject.
9. The human subject-specific pharmaceutical composition of item 5, wherein the antigen is selected from the antigens listed in Tables 2 to 7.
10. The human subject-specific pharmaceutical composition of item 1, wherein the at least two different polypeptides further comprise up to 10 amino acids flanking the T cell epitope that
10 are part of a consecutive sequence flanking the epitope in a corresponding antigen.
11. The human subject-specific pharmaceutical composition of item 1, 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.
12. The human subject-specific pharmaceutical composition of item 1, wherein two of the at least
15 two polypeptides are arranged end to end or overlapping in a joined polypeptide.
13. The human subject-specific pharmaceutical composition of item 12, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other.
14. The human subject-specific pharmaceutical composition of item 13, wherein the joined
20 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;
25 or

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

15. The human subject-specific pharmaceutical composition of item 1, 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

5 (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.

16. The human subject-specific pharmaceutical composition of item 1, further comprising a pharmaceutically acceptable diluent, carrier, preservative, or combination thereof.

17. The human subject-specific pharmaceutical composition of item 1, wherein the adjuvant is
10 selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosphamide, bacillus Calmette-Guerin (BCG), corynebacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenzene (DNCB), keyhole limpet hemocyanins (KLH), Freund's adjuvant (complete), Freund's adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria
15 toxin (DT), and combinations thereof.

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

(i) one or more 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 the subject and/or at least three HLA class II molecules of the subject; and

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

19. The kit of item 18, 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, wherein the amino acid sequence of the T cell epitope of each of the different polypeptides are different
25 from each other.

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

21. 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 the subject and/or at least three HLA class II molecules of the subject, 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.

22. The pharmaceutical composition of item 21, wherein the nucleic acid molecule expresses 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 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 the subject and/or at least three HLA class II molecules of the subject, wherein the amino acid sequence of the T cell epitope of each of the different polypeptides are different from each other.

23. A human subject-specific pharmaceutical composition for treatment of a disease or disorder in a specific human subject, comprising at least one different polypeptides, each of the at least one different polypeptides comprising at least a first region and a second region,

(i) the first region 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 the subject and/or at least three HLA class II molecules of the subject,

(ii) the second region 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 the subject and/or at least two HLA class II molecules of the subject,

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

24. The human subject-specific pharmaceutical composition of item 23, 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.
25. The human subject-specific pharmaceutical composition of item 23, comprising 2-40
5 different polypeptides.
26. The human subject-specific pharmaceutical composition of item 23, 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.
- 10 27. The human subject-specific pharmaceutical composition of item 23, wherein the epitopes of the first and second regions are from a single antigen.
28. The human subject-specific pharmaceutical composition of item 23, wherein the epitopes of the first and second regions are from two or more different antigens.
29. The human subject-specific pharmaceutical composition of item 27, wherein the antigen is an
15 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.
30. The human subject-specific pharmaceutical composition of item 29, wherein the cancer cell is
20 from the subject.
31. The human subject-specific pharmaceutical composition of item 27, wherein the antigen is selected from the antigens listed in Tables 2 to 7.
32. The human subject-specific pharmaceutical composition of item 23, wherein the polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the
25 two regions 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

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

33. The human subject-specific pharmaceutical composition of item 23, wherein the at least one polypeptides do not comprise any amino acid sequences that

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

10 (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.

34. The human subject-specific pharmaceutical composition of item 23, further comprising a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof.

35. The human subject-specific pharmaceutical composition of item 34, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosphamide,
15 bacillus Calmette-Guerin (BCG), corynebacterium parvum, levamisole, azimezone, isoprinosine, dinitrochlorobenzene (DNCB), keyhole limpet hemocyanins (KLH), Freund's adjuvant (complete), Freund's adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

20 36. A method of preparing a human subject-specific pharmaceutical composition for use in a method of treatment of a specific human subject, the method comprising:

(i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by

a) determining whether the fragment comprises:

25 1) an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; or

- 2) an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject; or
- 3) or meets both requirements (1) and (2); and
- b) identifying the sequence as a fragment of the polypeptide that is immunogenic for the
5 subject;
- (ii) selecting a first sequence of up to 50 consecutive amino acids of the polypeptide, which consecutive amino acids comprise the amino acid sequence of the fragment selected in step (i); and
- (iii) preparing a subject-specific pharmaceutical composition having as active ingredients one
10 or more polypeptides that together have all of the amino acid sequences selected in the preceding steps.
37. The method of item 36, further comprising prior to the preparing step repeating steps (i) to (ii) to select a second amino acid sequence of up to 50 consecutive amino acids of the same or a different polypeptide to the first amino acid sequence.
- 15 38. The method of item 37, further comprising, further repeating prior to the preparing step, steps (i) to (ii) one or more times to select one or more additional amino acid sequences of up to 50 consecutive amino acids of the same or different polypeptides to the first and second amino acid sequences.
39. The method of item 36, further comprising prior to the preparing step selecting a longer
20 fragment of the polypeptide if the fragment selected in step (i) is an HLA class I-binding epitope, which longer fragment comprises the fragment selected in step (i); and is a T cell epitope capable of binding at least three HLA class II molecules of the subject.
40. The method of item 36, wherein each polypeptide either consists of one of the selected amino acid sequences, or comprises or consists of two or more of the selected amino acid sequences
25 arranged end to end or overlapping in a single joined polypeptide.

41. The method of item 36, wherein any neoepitopes formed at the junction between any two of the selected amino acid sequences arranged end to end in a single joined polypeptide have been screened to eliminate substantially all polypeptides comprising a neoepitope amino acid sequence that
- 5 (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 two HLA class I molecules of the subject;
or
(iii) meets both requirements (i) and (ii).
- 10 42. The method of item 36, 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.
- 15 43. The method of item 36, further comprising determining HLA class I genotype and HLA class II genotype from a biological sample of the subject prior to step (i).
44. The method of item 43, wherein the determining HLA class I genotype and HLA class II genotype is performed by sequence based typing (SBT) methods.
- 20 45. The method of item 43, wherein the determining HLA class I genotype and HLA class II genotype is performed by sequencing, next generation sequencing, sequence specific primer (SSP) methods, or sequence specific oligonucleotide (SSO) methods.
46. The method of item 43, wherein the biological sample is blood, serum, plasma, saliva, buccal swab, urine, expiration, cell, or tissue.
- 25 47. The method of item 43, wherein the biological sample is saliva or a buccal swab.
48. A method of treating a cancer in a specific human subject in need thereof comprising,

administering to a specific human subject a pharmaceutical composition comprising at least one polypeptide,

each of the at least one polypeptide being 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 the subject and/or at least three HLA class II molecules of the subject,

wherein the T cell epitope of each of the at least one polypeptide is from an antigen that is specific for the cancer.

49. The method of item 48, 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, wherein the amino acid sequence of the T cell epitope of each of the different polypeptides are different from each other, and are from one or more antigens that are expressed by a cancer cell from the subject.

50. The method of item 48, wherein the composition comprises 2-40 different polypeptides.

51. The method of item 48, wherein 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.

52. The method of item 48, wherein the composition comprises at least two different polypeptides and the epitopes of the amino acid sequences of the at least two different polypeptides are from a single antigen.

53. The method of item 48, wherein the composition comprises at least two different polypeptides and the epitopes of the at least two different polypeptides are from two or more different antigens.

54. The method of item 48, wherein the one or more antigen is a neoantigen expressed by a cancer cell, a cancer-associated antigen, or a tumor-associated antigen.

55. The method of item 48, wherein the one or more antigen is selected from the antigens listed in Table 2.
56. The method of item 48, wherein the at least one different polypeptides further comprise up to 10 amino acids flanking the T cell epitope that are part of a consecutive sequence flanking the epitope in a corresponding antigen.
57. The method of item 48, wherein the at least one 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.
58. The method of item 48, wherein the composition comprises at least two different polypeptides and two of the polypeptides are arranged end to end or overlapping in a joined polypeptide.
59. The method of item 58, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other.
60. The method of item 59, 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).
61. The method of item 48, wherein the at least one polypeptide does 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.

62. The method of item 48, wherein the composition further comprises a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof.
63. The method of item 62, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosphamide, bacillus Calmette-Guerin (BCG), corynebacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenzene (DNCB), keyhole limpet hemocyanins (KLH), Freund's adjuvant (complete), Freund's adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.
64. The method of item 48, further comprising administering a chemotherapeutic agent, a targeted therapy, radiation therapy, a checkpoint inhibitor, another immunotherapy, or combination thereof.
65. A human subject-specific pharmaceutical composition for treatment of a disease or disorder in a specific human subject, 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 the subject and/or at least three HLA class II molecules of the subject; and (b) a pharmaceutically-acceptable adjuvant.
66. The human subject-specific pharmaceutical composition of item 65, 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 the subject and/or at least three HLA class II molecules of the subject, wherein the amino acid sequence of the T cell epitope of each of the different polypeptides are different from each other.
67. The human subject-specific pharmaceutical composition of item 66, comprising 2-40 different polypeptides.

68. The human subject-specific pharmaceutical composition of item 65, 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.

5 69. The human subject-specific pharmaceutical composition of item 66, comprising at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are from a single antigen.

70. The human subject-specific pharmaceutical composition of item 66, comprising at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are
10 from two or more different antigens.

71. The human subject-specific pharmaceutical composition of item 69, 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
15 expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen.

72. The human subject-specific pharmaceutical composition of item 71, wherein the cancer cell is from the subject.

73. The human subject-specific pharmaceutical composition of item 69, wherein the antigen is selected from the antigens listed in Tables 2 to 7.

20 74. The human subject-specific pharmaceutical composition of item 69, comprising at least two different polypeptides, wherein two of the polypeptides are arranged end to end or overlapping in a joined polypeptide.

75. The human subject-specific pharmaceutical composition of item 65, wherein the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosphamide,
25 bacillus Calmette-Guerin (BCG), corynebacterium parvum, levamisole, azimezone, isoprinosone,

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

- 5 76. The human subject-specific pharmaceutical composition of item 65, 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.
77. The human subject-specific pharmaceutical composition of item 76, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise
10 different epitopes from each other.
78. The human subject-specific pharmaceutical composition of item 77, wherein the joined polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the two polypeptides and that
15 (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).
79. The human subject-specific pharmaceutical composition of item 66, wherein the at least two
20 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.
80. A kit comprising:
25 (a) a first human subject-specific pharmaceutical 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 the subject and/or at least three HLA class II molecules of the subject; and (ii) a pharmaceutically-acceptable adjuvant;

- (b) a second human subject-specific pharmaceutical 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 the subject and/or at least three HLA class II molecules of the subject; and (ii) a pharmaceutically-acceptable adjuvant, wherein the first and second polypeptides comprise different T cell epitopes.

81. The kit of item 77, 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 the subject and/or at least three HLA class II molecules of the subject, wherein the amino acid sequences comprise different T cell epitopes.

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.

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

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.

5 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
10 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).

15 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)	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.

- 5 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 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.

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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, 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. 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).

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Table 17. Clinical trials conducted with peptide vaccines.

<i>Peptide vaccines</i>	<i>Source antigen</i>	<i>Peptide length</i>	<i>T cell assay</i>	<i>Pop. (n)</i>	<i>Ethnicity</i>	<i>Ref.</i>
MMNLMQPKTQQTYTYD	JUP	16mer	Multimer staining	18	Canadian	¹²
GRGSTTTNYLLDRDDYRNTSD	ADA17	21mer	Multimer staining	18	Canadian	¹²
LKKGAAADGGKLDGNAKLNRSLK	BAP31	22mer	Multimer staining	18	Canadian	¹²
FPPKDDHTLKFYDDNQRPYPP	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
STAPPAHGVTSPDTRPAPGSTAPP	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). We also found a linear correlation between ≥ 1 PEPI3+ Score and response rate ($R^2 = 0.77$) (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 18. Comparison of ≥ 1 PEPI3+ Scores and CTL response rates of 12 peptide vaccines.

<i>Peptide vaccine</i>	<i>Source antigen</i>	<i>Response rate (Clinical Trials)</i>	≥ 1 PEPI3+ Score* (Model Population)	<i>OPA</i>
MMNLMQPKTQQTYTYD	JUP	0%	22%	NA
GRGSTTTNYLLDRDDYRNTSD	ADA17	11%	18%	61%
LKKGAADGGKLDGNAKLNRSK	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 19. 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)	checkpo int 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 20. 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

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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 21).

Table 21. Immune Response Rates in the Model Population and in two clinical trials to IMA901

Immune responses to TUMAPs	Model Population (HLA-A2+) (n=180)	Phase I (n=27)*	Phase II (n=64)*
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

A correlation 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 22). 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 23 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 ($R^2 = 0.76$) (FIG. 9).

Table 22. 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	Immaties	Renal cell cancer	28	CEU	A02	i.d.	0.4	8x in 10 wks	12	19
IMA901 phase II	9 TAAs	Immaties	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
Immunin	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 of 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 criteria⁴⁵

Table 23. 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%
TSPV 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%

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Example 13 – The set of multiple HLA binding peptides from tumor antigens predicts responders to the checkpoint inhibitor immunotherapy Ipilimumab

Whether survival benefit of melanoma patients treated with the checkpoint inhibitor Ipilimumab can be predicted by the number of melanoma-specific PEPI3+s that are potentially expressed in the patient's tumor was determined.

Eighty melanoma associated antigens (TAAs) were identified from which a panel of PEPI3+s (IPI-PEPI panel: 627 PEPIs) that are shared by Ipilimumab treated melanoma patients with a prolonged clinical benefit and are absent in those without a prolonged benefit was selected. These PEPI3+ define the specific T cells that are re-activated by Ipilimumab to attack the patient's tumor cells. Patients with certain HLA sequences that can present more melanoma-specific PEPIs have more T cells re-activated by Ipilimumab and a higher chance to benefit from Ipilimumab immunotherapy.

The clinical benefit from Ipilimumab treatment for 160 patients from four independent clinical trial cohorts was determined. Two cohorts were from the trials CA184-007 (10 mg/kg

Ipilimumab) and CA184-002 (3 mg/kg Ipilimumab) and two cohorts from published clinical trials 10 mg/kg and 3/mg/kg Ipilimumab datasets^{5, 38, 39}.

Epitopes from 80 melanoma antigens restricted to all the 6 HLA class I of each patient were predicted and the number of melanoma-specific PEPI3+s restricted to at least 3 class I
 5 HLAs of each patient (4,668 PEPIs) was then computed. Each patient with at least one out of 627 PEPIs qualified as responder. The IPI-PEPI panel predicts the overall survival of both 10 mg/kg and 3 mg/kg Ipilimumab. Results were highly significant and consistent in the four independent cohort (Fig. 10).

Example 14: Multiple HLA binding epitopes define patient mutational neoantigens

10 The capability of the PEPI3+ to identify neoantigens from mutations was determined. PEPI3+s of 110 melanoma patients treated with Ipilimumab was determined using published exome mutation data³⁹. From the exome mutation data, mutations in 9,502 antigens from the 110 patients (Fig. 11A). Median nonsynonymous mutational load per sample was highly variable, 309 (29–4,738) in the clinical benefit cohort and 147 (7–5,854) in the minimal or no clinical
 15 benefit cohort. Due to their epitope prediction results these mutations had 211 (8-1950) and 56 (2-3444) neoepitopes in the clinical benefit cohort and the minimal or no clinical benefit cohorts, respectively.

Mutational PEPI3+ neoepitopes from the published mutations were determined (Fig. 11B and Table 24). These mutations resulted in median 16 PEPIs and 6 PEPIs neoepitopes in clinical
 20 benefit cohort and the minimal or no clinical benefit cohorts, respectively.

Results show that PEPIs define the mutational neoantigens derived from genetically altered proteins expressed in an individual. Such neoantigens are PEPI3+ peptides that capable to activate T cells in the patient's body. If a genetic alteration occurs in the tumor cell of the individual that creates a PEPI3+ then this PEPI3+ can induce T cell responses. These PEPI3+
 25 containing peptides could be included in a drug (e.g. vaccine, T cell therapy) to induce immune response against the individual tumor.

Table 24. Mutational neoantigen prediction using PEPI Test: Analysis results of Van Allen et al. and PEPI Test on 110 melanoma patients.

Parameters	Results published by Van Allen et al.		Result obtained from PEPI Test analyses (Validated epitopes and PEPIs)	
Patients	Clinical benefit (n=27)	Minimal or no clinical Benefit (n=73)	Clinical benefit (n=27)	Minimal or no clinical benefit (n=73)
Median mutations	555	281	-	-
Median nonsynonymous mutations	309	147	-	-
Median expressed mutational antigens	198		-	-
Median neoepitope (only 9mer)	211	56	130	50
Recurrent neoepitopes	28	Not provided	10	76
Median PEPI neoepitopes	-	-	16	6
Recurrent PEPI neoepitopes	-	-	1	5

Example 15 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%
<i>In silico</i> study (PEPI3+ Test)	4/433	1%

An HLA map of the Rindopepimut on the HLA alleles of the subjects in the Model Population (Fig. 12) 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 15

- 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 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.
- 10 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.
- 15 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.
- 20 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 et 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.
- 25

Example 16. 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).

30

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 sporadically identified in some subjects also in the C terminal region. However, these 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 disclosure 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 17 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 19 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%	ANSVVSDDMMVSIMKTLKIQV	3	4
POC01_P10	MAGE-A4	37%	REALSNKVDELAHFLLRKYR	3	2
POC01_P11	MAGE-A9	37%	ETSYEKVINYLVMNLNAREPI	3	4
POC01_P12a	MAGE-A10	52%	DVKEVDPTGHSEFVLVTSGL	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. 13. 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 synthesized, 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			
		1 st cycle	2 nd cycle	3 rd cycle	4 th 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
- 5 • 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
- 10 • **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
- 15 • 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 14.

20 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 18 Design of Personalised Immunotherapy Composition for Treatment of Breast Cancer

- 25 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 15.

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%	SAVFHERYALIQHQBTHKNE	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%	MASFRKLTLSSEKVPNHPSPR	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: Etrazole, Ibrance (Palbociclib) and Zoladex

Results

5 **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

- 10 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:

- 15 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 Palbociclib since spring/summer. Patient ABC passed away in Jan 2018.

- 20 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. Palbociclib 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.

- 25 Example 19 - Personalised Immunotherapy Composition for treatment of patient with late stage metastatic breast cancer Patient BRC05 was diagnosed with inflammatory breast cancer on the right with extensive lymphangiosis carcinomatosa. 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).
30 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 Virus¹. Indeed, HPV16 DNA was diagnosed in the tumor of this patient.

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

- 5 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.

- 10 14 vaccine peptides were designed and prepared for patient BRC05 (Table 30). Peptides PBRC05-P01-P10 were made for this patient based on population expression data. The last 3 peptides in the Table 29 (SSX-2, MORC, MAGE-B1) were designed from antigens that expression was measured directly in the tumor of the patient.

Table 30 – 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

- 15 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 31 - 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

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.

10 Example 20 - Personalised Immunotherapy Composition for treatment of patient with early stage metastatic breast cancer

HISTORY: In 2011 left breast sector excision due to neoplasm. Treatment: aromatase inhibitor and lumbar spine irradiation (osseal mets).

15 In 2017, before PIT vaccine treatment was administered, a metastatic lesion was observed on the ventral bow of the right 5th rib and in the right 3rd rib. In the left breast recurrent malignancy has to be ruled out. In the right breast a malignancy with metastatic right axillary lymph node may exist.

Table 32 - Vaccine peptides for patient of Example 20

Patient's vaccine peptides	Target Antigen	Antigen Expression	20mer peptide	MAXHL A CD8	MAXHL A CD4
PBRC04_P1	SPAG9	88%	XXXXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P2	AKAP4	85%	XXXXXXXXXXXXXXXXXXXXXX	4	4
PBRC04_P3	BORIS	71%	XXXXXXXXXXXXXXXXXXXXXX	3	2
PBRC04_P4	MAGE-A11	59%	XXXXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P6	NY-SAR-35	49%	XXXXXXXXXXXXXXXXXXXXXX	3	5
PBRC04_P7	FSIP1	49%	XXXXXXXXXXXXXXXXXXXXXX	3	6
PBRC04_P8	NY-BR-1	47%	XXXXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P10	LDHC	35%	XXXXXXXXXXXXXXXXXXXXXX	3	5

PBRC04_P11	GATA-3	31%	XXXXXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P13	Survivin	71%	XXXXXXXXXXXXXXXXXXXXXXX	3	2
PBRC04_P14	MAGE-C1	12%	XXXXXXXXXXXXXXXXXXXXXXX	3	8
PBRC04_P15	PRAME	55%	XXXXXXXXXXXXXXXXXXXXXXX	3	5

The patient obtained 2 cycles of PIT vaccine.

Example 21 - Characterization of toxicity – immunoBLAST

A method was developed for performing on any antigen to determine its potential to induce toxic immune reaction, such as 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 assessed using 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 16, 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 33. 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 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 33 - 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	
	PVSEGKSR	150	34.6%	X		0	0.0%		
	VSEGKSR	194	44.8%	X		1	0.2%	X	
	SEGKSR	113	26.1%	X		0	0.0%		
	EGKSR	77	17.8%	X		0	0.0%		
	GKSR	37	8.5%	X		0	0.0%		
	KSR	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%		
	ARTAKKVR	134	30.9%	X		0	0.0%		
	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%		
	LMVGLKDH	97	22.4%	X		0	0.0%		

PolyPEPI1 018 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
	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%		
	TKKFQKVN	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

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 Gudmundsdottir 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=init>The 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. Multi-peptide 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 multi-peptide melanoma vaccine. *J Clin Oncol.* 2011;29(21):2924-32.
- ²⁴ Kaida et al. Phase I 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 identifying a fragment of a polypeptide as immunogenic for a specific human subject or predicting whether a polypeptide or a fragment of a polypeptide is immunogenic for a specific human subject, the method comprising the steps of
 - (i) determining whether the polypeptide comprises:
 - (a) an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; or
 - (b) an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject; and
 - (ii) (I) identifying said sequence as a fragment of the polypeptide that is immunogenic for the subject; or
 - (II) predicting
 - A. that the polypeptide is immunogenic for the subject if the polypeptide comprises at least one sequence that meets the requirements of step (i); or
 - B. 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).
2. The method of claim 1, wherein:
 - (a) the T cell epitope is capable of binding to at least three HLA class I molecules of the subject and consists of 9 consecutive amino acids of the polypeptide, or wherein the T cell epitope is capable of binding to at least three HLA class II molecules of the subject and consists of 15 consecutive amino acids of the polypeptide;
 - (b) step (i) comprises determining that the polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject;
 - (c) step (i) comprises determining that the polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject; and/or
 - (d) step (i) comprises determining that the polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject and identifying a fragment of the polypeptide that is a T cell epitope capable of binding to at

least one HLA class II molecule of the subject, wherein the HLA class II-binding epitope comprises the amino acid sequence of the HLA class I-binding T cell epitope.

3. The method of claim 1 or claim 2, wherein the polypeptide
 - (a) is expressed by a pathogenic organism, a virus or a cancer cell, is associated with an autoimmune disorder, or is an allergen or an ingredient of a pharmaceutical composition;
 - (b) is selected from the antigens listed in Tables 2 to 6;
 - (c) is an antigen or neoantigen expressed by a cancer cell, optionally wherein the cancer cell, the antigen or the neoantigen is in a sample taken from the subject;
 - (d) is a mutational neoantigen, optionally wherein
 - A. the neoantigen is present in a sample obtained from the subject; and/or
 - B. the immunogenic fragment comprises a neoantigen specific mutation; or
 - (e) is associated with or suspected of being associated with an autoimmune disorder or an autoimmune response in the subject, wherein determining that the polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject identifies the polypeptide and/or the fragment as immunogenic or associated with the autoimmune disorder or autoimmune response in the subject.
4. The method of any one of claims 1 to 3, wherein all of the fragments of the polypeptide that are a T cell epitope capable of binding to at least three HLA class I molecules and/or all of the fragments of the polypeptide that are a T cell epitope capable of binding to at least three HLA class II molecules of the subject are identified, optionally wherein the method is repeated for each polypeptide that is an active ingredient of a specific pharmaceutical composition.
5. The method of any one of the preceding claims, further comprising predicting whether the subject will have a cytotoxic T cell response or a helper T cell response to administration of one or more polypeptide or a pharmaceutical composition or kit comprising one or more polypeptides as active ingredients, wherein
 - A. a cytotoxic T cell response is predicted if the polypeptide(s) comprises at least one amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject;

B. a helper T cell response is predicted if the polypeptide(s) comprises at least one amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject;

C. no cytotoxic T cell response is predicted if the polypeptide(s) does not comprise any amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; or

D. no helper T cell response is predicted if the polypeptide(s) does not comprise any amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject.

6. The method of claim 5, wherein the method further comprises determine the likelihood that the subject will have a cytotoxic T cell response and/or a helper T cell response that targets a polypeptide antigen that is expressed in the subject, the method comprising

(i) identifying one or more polypeptide antigens that comprises an amino acid sequence that is

(a) a T cell epitope capable of binding to at least three HLA class I or at least three HLA class II molecules of the subject; and

(b) comprised in the amino acid sequence of the polypeptide(s); and

(ii) using population expression frequency data for the one or more polypeptide antigens identified in step (i) to determine the likelihood that the subject will have a cytotoxic T cell response and/or a helper T cell response that targets a polypeptide antigen that is expressed in the subject.

7. The method of claim 5, wherein the polypeptide is a component of a pharmaceutical composition and the method comprises determining the likelihood that the subject will develop anti-drug antibodies (ADA) following administration of the polypeptide, wherein a predicted T helper cell response corresponds to a higher likelihood of ADA and no predicted T helper cell response corresponds to a lower likelihood of ADA, optionally wherein the polypeptide is a checkpoint inhibitor.

8. The method of any one of claims 1 to 6 further comprising predicting whether the subject will have a clinical response to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, the method comprising

determining 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 three HLA class I molecules of the subject; and predicting

A. that the subject will have a clinical response to administration of the pharmaceutical composition, kit or panel of polypeptides if the one or more active ingredient polypeptides 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; or

B. that the subject will not have a clinical response to administration of the pharmaceutical composition, kit or panel of polypeptides if the one or more active ingredient polypeptides together comprise no more than one sequence that 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).

9. The method of any one of claims 1 to 6 and 8, further comprising determining the likelihood that the specific human subject will have a clinical response to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, wherein one or more of the following factors corresponds to a higher likelihood of a 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 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 an active ingredient polypeptide; and

B. a T cell epitope capable of binding to at least three HLA class I of the subject.

10. The method of any one of claims 1 to 6, 8 and 9, further comprising determining the likelihood that the specific human subject will have a clinical response to administration of a pharmaceutical composition, kit or panel of polypeptides comprising one or more polypeptides as active ingredients, wherein the method comprises

(i) identifying which polypeptide antigens targeted by the active ingredient polypeptide(s) comprise an 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;

(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), optionally using population expression data for each antigen identified in step (i) to determine the probability that the subject expresses two or more of the antigens identified in step (i) that together comprise at least two different amino acid sequences of step (i), further 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); and

(iii) determining the likelihood that the subject will have a clinical response to 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.

11. The method of claim 9 or claim 10, wherein one or more of the following factors correspond to a higher likelihood of a 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 II 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 II of the subject, optionally wherein the target polypeptide antigens are expressed in the subject, optionally wherein the target polypeptides antigens are in one or more samples obtained from the subject;

(c) a higher number of target polypeptide antigens comprising

i. 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; and

ii. 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 II of the subject;

(d) a higher probability that the subject expresses target polypeptide antigens, optionally a threshold number of the target polypeptide antigens, that have been determined to comprise 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 II of the subject

(e) a higher probability that the subject expresses target polypeptide antigens, optionally a threshold number of the target polypeptide antigens, that have been determined to comprise

i. 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; and

ii. 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 II of the subject;

(f) 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 that have been determined to comprise 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 II of the subject; and/or

(g) 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 that have been determined to comprise

i. 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; and

ii. 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 II of the subject.

12. The method of claim 6, further comprising repeating the method for one or more further pharmaceutical compositions, kits or panels of polypeptides and ranking the compositions, kits or panels of polypeptides by their likelihood to induce a clinical response in the subject.

13. The method of any one of claims 1 to 12, further comprising predicting whether administration of the polypeptide, pharmaceutical composition, kit or panel of polypeptides will induce a toxic immune response in the subject, wherein

(a) the polypeptide(s) comprises at least one amino acid sequence that

- i. is capable of binding to at least three HLA class I of the subject; and
- ii. corresponds to a fragment of a human polypeptide expressed in healthy cells;

and a toxic immune response is predicted; or

(b) the polypeptide(s) do not comprise any amino acid sequence that

- i. is capable of binding to at least three HLA class I of the subject; and
- ii. corresponds to a fragment of a human polypeptide expressed in healthy cells;

and no toxic immune response is predicted.

14. The method of any one of the preceding claims further comprising selecting or recommending for treatment of the specific human subject administration to the subject of a polypeptide that comprises a polypeptide fragment that is identified as immunogenic for the subject, or of a polypeptide that is predicted to be immunogenic, or to induce a cytotoxic T cell or helper T cell response, or of a pharmaceutical composition, kit or panel of polypeptides that is predicted to induce a clinical response, or of a polypeptide or pharmaceutical composition that is predicted not to induce a toxic immune response or not to induce ADA in the subject.

15. The method of any one of claims 1 to 4 further comprising predicting whether the subject will have a clinical response to administration of a checkpoint inhibitor to treat cancer, the method comprising determining whether one or more cancer associated antigens together comprise at least two different amino acid sequences each of which is a T cell epitope capable of binding to at least three HLA class I of the subject and predicting

A. that the subject will have a clinical response to administration of a checkpoint inhibitor if the one or more cancer associated antigens 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; or

B. that the subject will not have a clinical response to administration of a checkpoint inhibitor if the one or more cancer associated antigens together comprise no more than one

sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject.

16. The method of any one of claims 1 to 4 and 15, wherein the method further comprises determining the likelihood that the subject will have a clinical response to administration of a checkpoint inhibitor to treat cancer, the method comprising

- (i) selecting a plurality of polypeptide antigens that are associated with the cancer type of the subject;
- (ii) identifying which of said cancer associated antigens comprise an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; and
- (iii) using population expression data for each cancer associated antigen identified in step to determine the likelihood that the subject will have a clinical response to administration of a checkpoint inhibitor to treat cancer, wherein a higher probability that the subject expresses one or more of the cancer associated antigens identified in step (ii) that together comprise at least two amino acid sequences each of which is a T cell epitope capable of binding to at least three HLA class I molecules of the subject corresponds to a more likely clinical response.

17. The method of claim 16 further comprising selecting or recommending administration of a checkpoint inhibitor for treatment of the subject.

18. Use of a checkpoint inhibitor in the preparation of a medicament for treating cancer in a human subject in need thereof, wherein the subject has been predicted to respond, or to be likely to respond, to administration of the checkpoint inhibitor by a method according to claim 16.

19. The method of any one of claims 5, 7, 8 and 15, wherein the subject has been predicted to have a toxic immune response or ADA development, or not to have a cytotoxic T cell or helper T cell or clinical response, or not to respond to treatment with a checkpoint inhibitor and the method further comprises selecting or recommending a different treatment for the subject.

20. An *in vitro* or *in silico* method of designing or preparing a human subject-specific pharmaceutical composition or kit or panel of polypeptides for treatment of a specific human subject, the method comprising:

- (i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by the method of any one of claims 1 to 3;
- (ii) selecting a first sequence of up to 50 consecutive amino acids of the polypeptide, which consecutive amino acids comprise the amino acid sequence of the fragment selected in step (i);
- (iii) repeating steps (i) and (ii) to select a second amino acid sequence of up to 50 consecutive amino acids of the same or a different polypeptide to the first amino acid sequence;
- (iv) optionally further repeating steps (i) and (ii) to select one or more additional amino acid sequences of up to 50 consecutive amino acids of the same or different polypeptides to the first and second amino acid sequences; and
- (v) designing or preparing a subject-specific pharmaceutical composition, kit or panel of polypeptides having as active ingredients one or more polypeptides that together have all of the amino acid sequences selected in the preceding steps, optionally wherein one or more or each sequence is flanked at the N and/or C terminus by additional amino acids that are not part of the sequence of the polypeptides.

21. The method of claim 20, wherein the the fragment selected in step (i) is an HLA class I-binding epitope, and the method further comprises selecting a longer fragment of the polypeptide, which longer fragment

- a. comprises the fragment selected in step (i); and
 - b. is a T cell epitope capable of binding at least three or to the most possible HLA class II molecules of the subject;
- and wherein the sequence of up to 50 consecutive amino acids selected in step (ii) comprises said longer sequence.

22. The method of claim 20 or 21, wherein each polypeptide either consists of one of the selected amino acid sequences, or comprises or consists of two or more of the selected amino acid sequences arranged end to end or overlapping in a single peptide, optionally wherein all of the neoepitopes formed at the join between any two of the selected amino acid sequences

arranged end to end in a single polypeptide have been screened to eliminate polypeptides comprising a neoepitope amino acid sequence that

- (a) corresponds to a fragment of a human polypeptide expressed in healthy cells;
- (b) is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; or
- (c) meets both requirements (a) and (b).

23. The method of any one of claims 20 to 22, wherein the one or more polypeptides have been screened to eliminate polypeptides comprising an amino acid sequence that

- (a) corresponds to a fragment of a human polypeptide expressed in healthy cells; or
- (b) corresponds to a fragment of a human polypeptide expressed in healthy cells and is a T cell epitope capable of binding to at least three HLA class I molecules of the subject.

24. Use of a pharmaceutical composition, kit or panel of polypeptides in the manufacture of a medicament for treating cancer in a specific human subject, wherein the pharmaceutical composition, kit or panel has been designed or prepared for treatment of the subject according to the method of any one of claims 20 to 23, and wherein each of the fragments selected in step (i) is a fragment of a different cancer associated antigen, optionally wherein the medicament is for prophylactic use in the subject.

25. The use of claim 24, wherein the polypeptide(s) of the medicament together comprises at least seven different T cell epitopes, each of which is capable of binding to at least three HLA class I molecules and/or at least three HLA class II molecules of the subject.

26. The use according to claim 24 or claim 25, wherein the cancer-associated antigens are selected from the antigens listed in Table 2.

27. The use according to any one of claims 24 to 26, wherein one or more or each of the cancer-associated antigen sequences is flanked at the N and/or C terminus by additional amino acids that are not part of the cancer-associated antigen amino acid sequence .

28. The use according to any one of claims 24 to 27, wherein one or more or each active ingredient peptide or polypeptide of the pharmaceutical composition, kit or panel of polypeptides either

(i) consists of a sequence of up to 50 consecutive amino acids from one of the cancer-associated antigens; or

(ii) comprises or consist of two or more of said sequences of up to 50 consecutive amino acids of the cancer-associated antigens arranged end to end or overlapping in a single peptide.

29. The use according to claim 28, wherein the one or more peptides or polypeptides do not comprise any neoepitopes that span a join between any two of said amino acid sequences that are arranged end to end in a single peptide and that

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

(2) is a T cell epitope capable of binding to at least three HLA class I molecules of the subject; or

(3) meets both requirements (1) and (2).

30. The use according to any one of claims 24 to 29, wherein the medicament is for administration in combination with chemotherapy, targeted therapy or a checkpoint inhibitor.

31. A method of designing or preparing a polypeptide for inducing an immune response in a specific human subject the method comprising selecting an amino acid sequence that 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 the subject, and designing or preparing a polypeptide comprising the selected amino acid sequence; optionally wherein the method is

(a) a method of designing or preparing a polypeptide for inducing a cytotoxic T cell response in a specific human subject, the method comprising selecting an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class I molecules of the subject, and designing or preparing a polypeptide comprising the selected amino acid sequence; or

(b) a method of designing or preparing a polypeptide for inducing a helper T cell response, the method comprising selecting an amino acid sequence that is a T cell epitope capable of binding to at least three HLA class II molecules of the subject, and designing or preparing a polypeptide comprising the selected amino acid sequence.