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(54) **PERSONALISED IMMUNOGENIC PEPTIDE IDENTIFICATION PLATFORM**

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(57) **ABSTRACT**

The disclosure relates to methods of identifying fragments of a polypeptide that are immunogenic for a specific human subject, methods of preparing personalised pharmaceutical compositions comprising such polypeptide fragments, human subject-specific pharmaceutical compositions comprising such polypeptide fragments, and methods of treatment using such compositions. The methods comprise identifying a fragment of the polypeptide that binds to multiple HLA of the subject.

Specification includes a Sequence Listing.

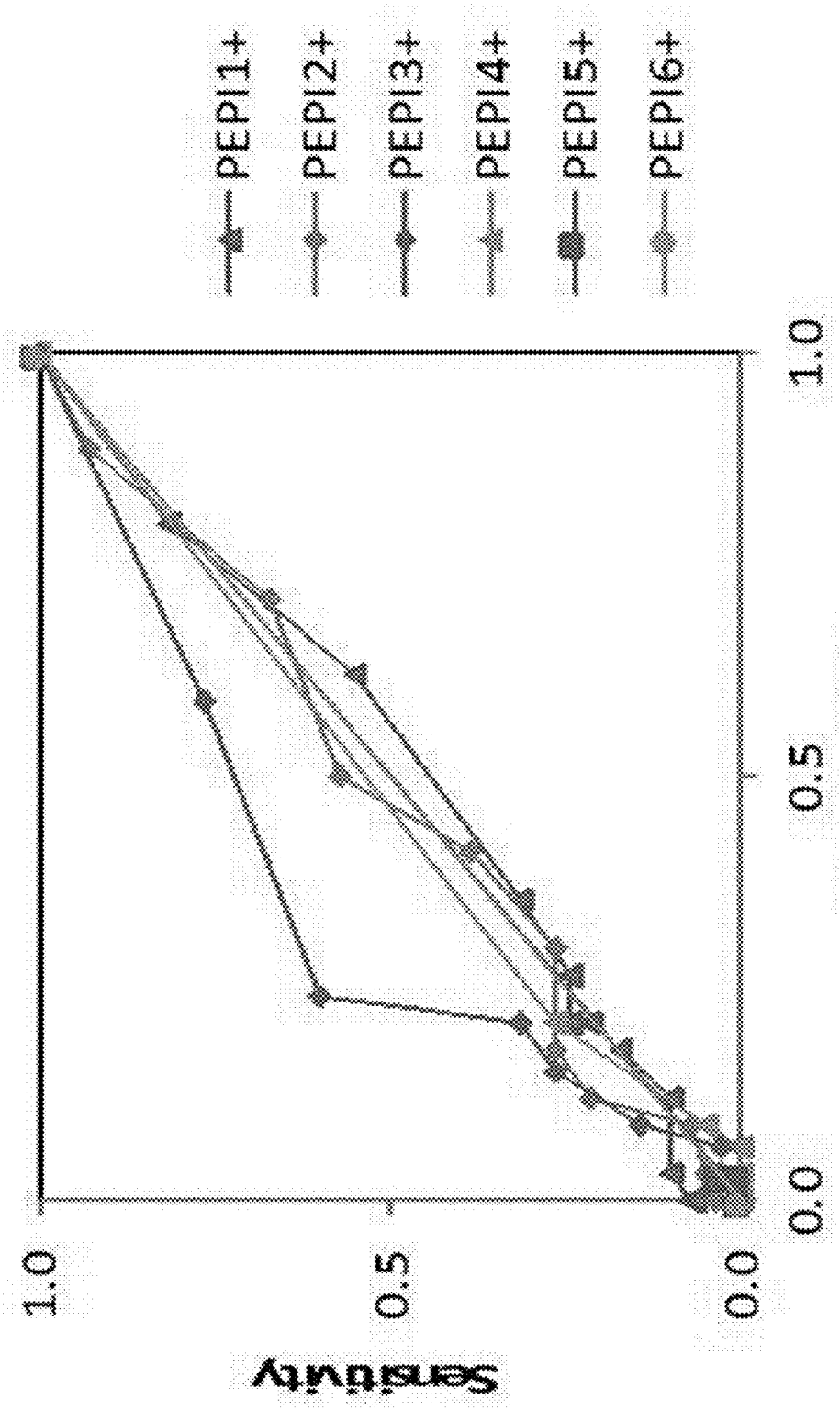
PEPI1+
PEPI2+
PEPI3+
PEPI4+
PEPI5+
PEPI6+
Sensitivity
1.0
0.5
0.0
0.0
0.5
1.0
1-Specificity

FIG. 1

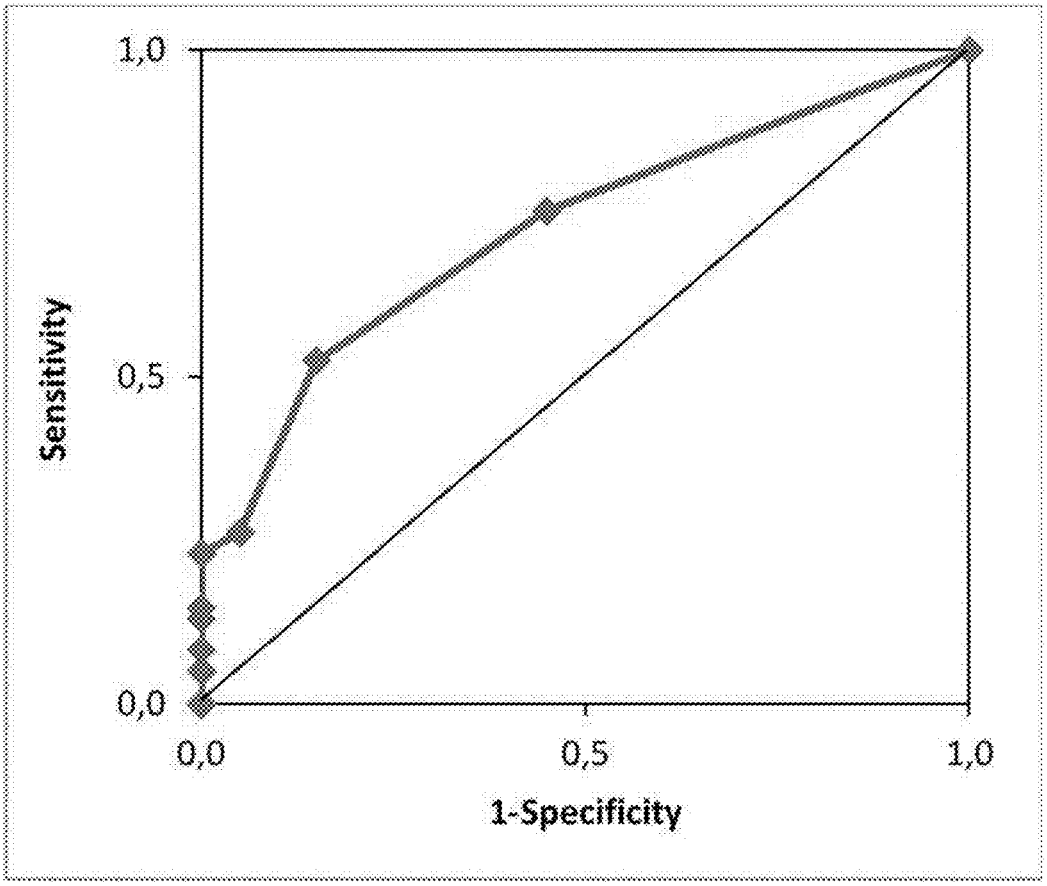

FIG. 2

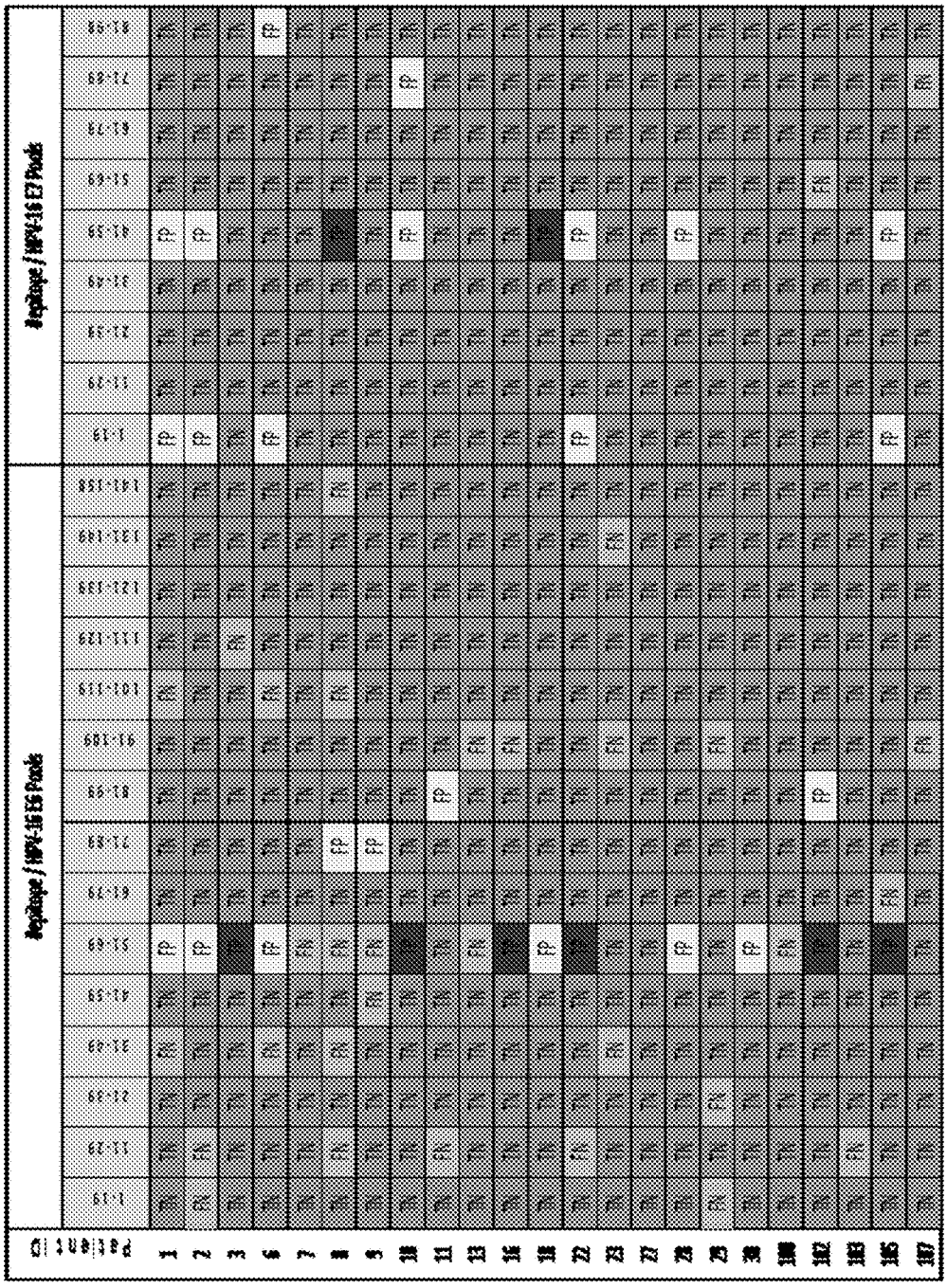

FIG. 3A

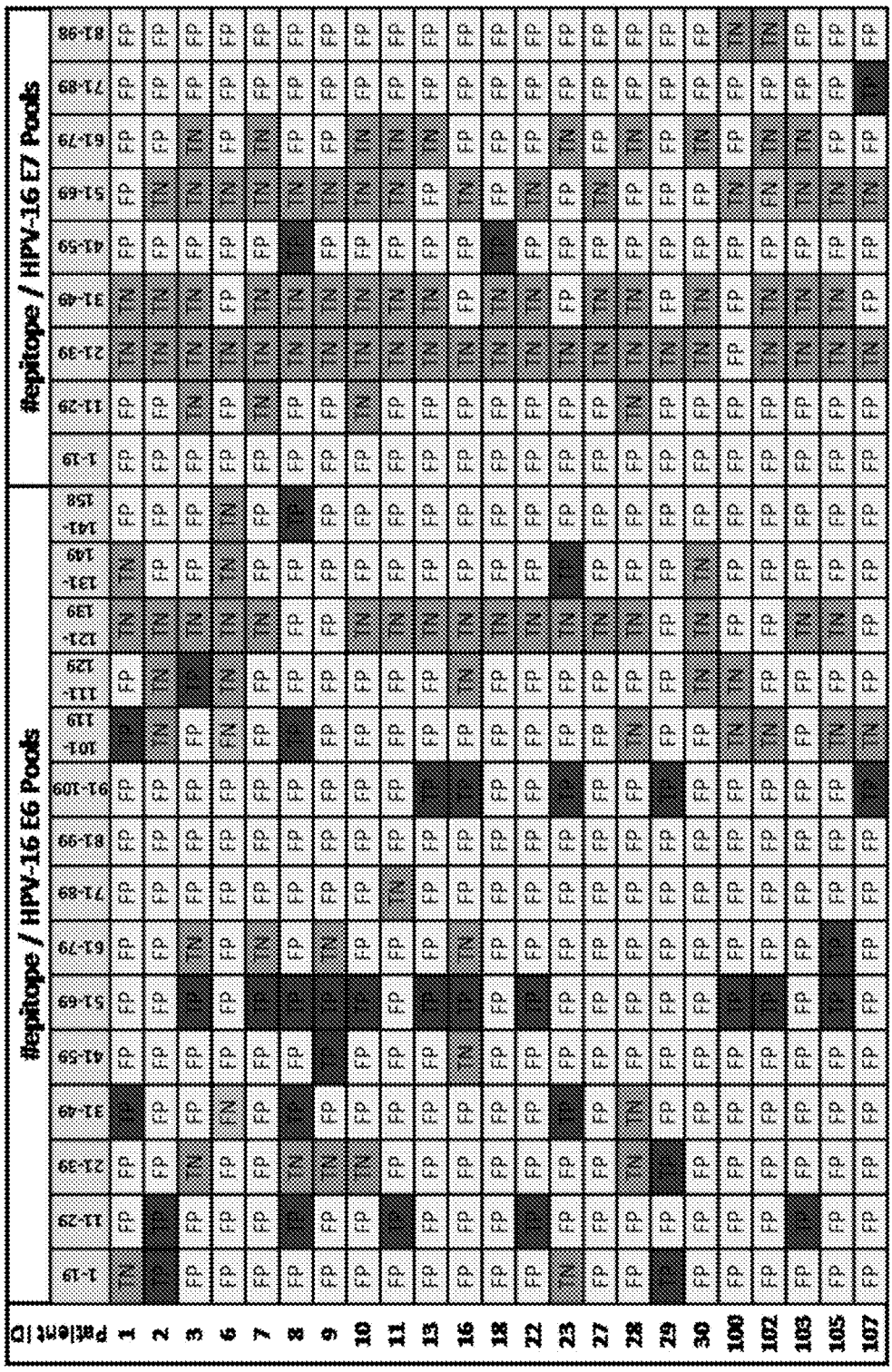
Patient ID
#epitope / HPV-16 E6 Pools
#epitope / HPV-16 E7 Pools
1-19
11-29
21-39
31-49
41-59
51-69
61-79
71-89
81-99
91-109
101-119
111-129
121-139
131-149
141-158
1-19
11-29
21-39
31-49
41-59
51-69
61-79
71-89
81-98
1
2
3
6
7
8
9
10
11
13
16
18
22
23
27
28
29
30
100
102
103
105
107

FIG. 3B

Pat ID	#PEPI / HPV-16 E6				E7	
	E6.1	E6.2	E6.3	E6.4	E7.1	E7.2
1	FP	TP	TP	FN	TN	FN
2	FP	TP	TP	TN	TN	TP
3	TP	TP	TP	TP	TN	TP
6	TP	TP	TP	FN	TP	TP
7	TP	TP	TP	TP	TN	TP
8	TP	TP	TP	FN	FP	TP
9	TP	TP	TP	FN	FP	TP
10	FP	TP	TP	FN	TN	TP
11	TP	TP	FN	FN	TN	TP
13	TP	TP	FN	FN	TN	FN
16	TP	TP	TP	FN	FP	TP
18	FP	TP	FN	FN	FN	TP
22	TP	TP	TP	FN	FN	FN
23	FP	TP	TP	FN	TN	TN
27	TP	TP	TP	FN	FN	FN
28	TP	TP	TP	FN	TN	FN
29	FP	TP	TP	FN	FP	TP
30	FP	FP	TN	TN	FN	FN
100	TP	TP	TP	FN	TN	TP
102	TP	TP	TP	FN	FN	TP
103	TP	TP	TP	FN	TN	TN
105	TP	TP	TP	TP	TN	TN
107	TP	TP	FN	FN	TN	FN

FIG. 4A

	# epitope / HPV-16 E6&E7 pools					
Patient ID	E6.1	E6.2	E6.3	E6.4	E7.1	E7.2
1	FP	TP	TP	FN	FP	TP
2	FP	TP	TP	TN	TN	TP
3	TP	TP	TP	FN	FP	TP
6	TP	TP	TP	FN	TP	TP
7	TP	TP	TP	FN	FP	TP
8	TP	TP	TP	FN	FP	TP
9	TP	TP	TP	FN	FP	TP
10	FP	TP	TP	FN	FP	TP
11	TP	TP	TP	FN	FP	TP
13	TP	TP	TP	FN	TN	TP
16	TP	TP	TP	FN	TN	TP
18	FP	TP	TP	FN	FN	TP
22	TP	TP	TP	FN	TP	TP
23	FP	TP	TP	FN	FP	FP
27	TP	TP	TP	FN	TP	TP
28	TP	TP	TP	FN	FP	TP
29	FP	TP	TP	FN	FP	TP
30	FP	FP	FP	TN	FN	TP
100	TP	TP	TP	FN	FP	TP
102	TP	TP	TP	FN	TP	TP
103	TP	TP	TP	FN	TN	FP
105	TP	TP	TP	FN	TN	FP
107	TP	TP	TP	FN	FP	TP

FIG. 4B

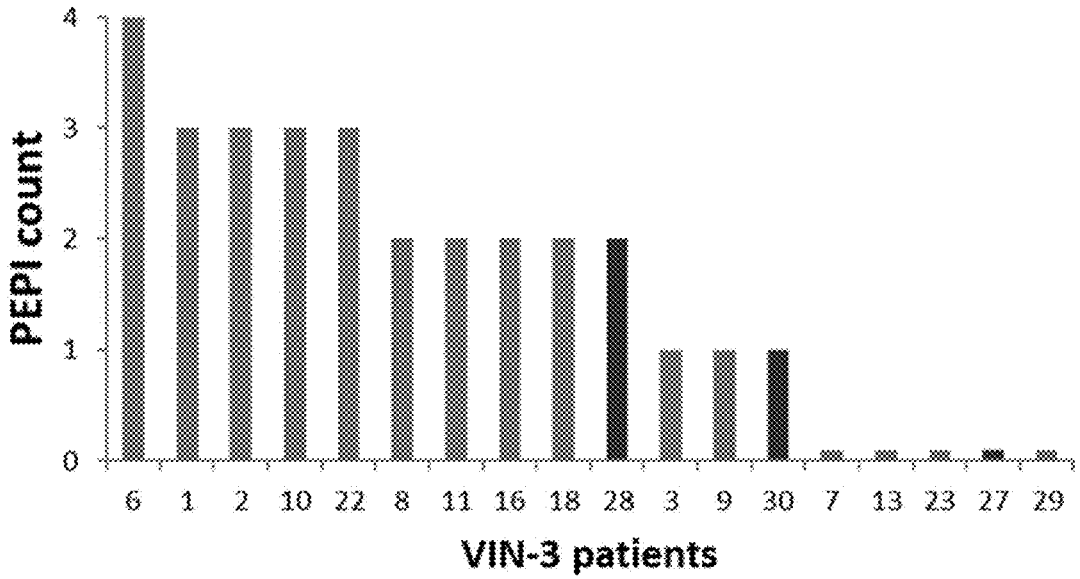
PEPI count
4
3
2
1
0
6 1 2 10 22 8 11 16 18 28 3 9 30 7 13 23 27 29
VIN-3 patients

FIG. 5A

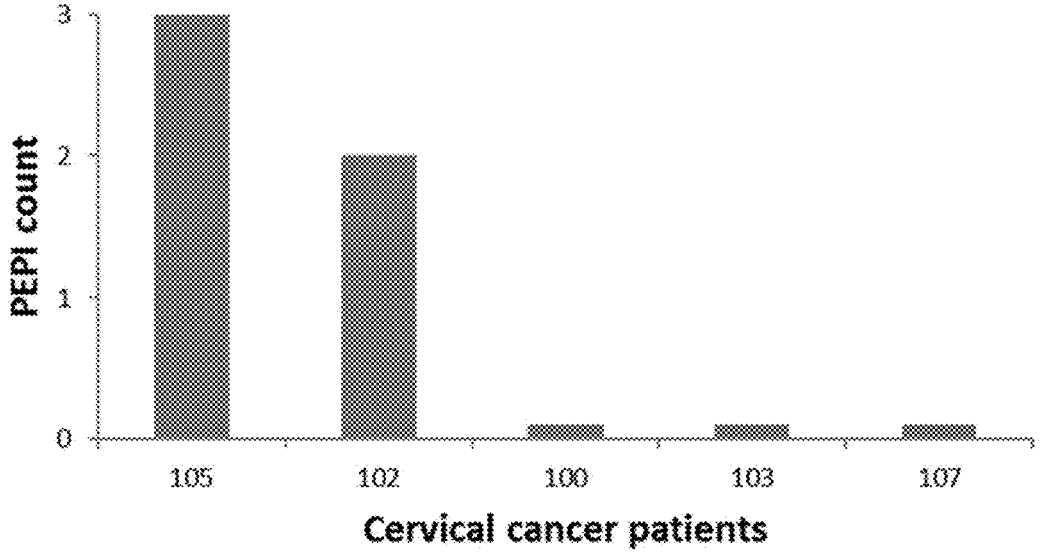
PEPI count
3
2
1
0
105 102 100 103 107
Cervical cancer patients

FIG. 5B

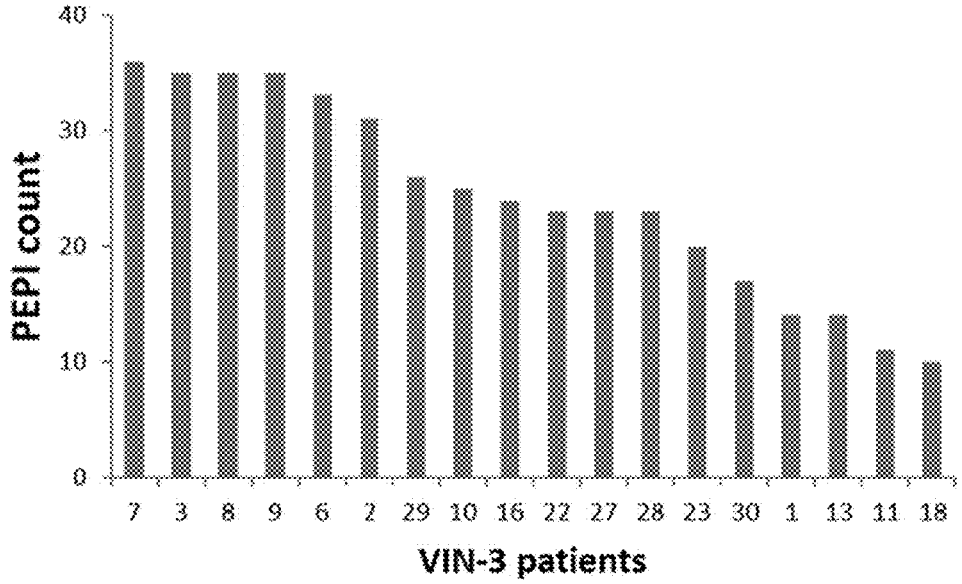
40
30
20
10
0
PEPI count
7 3 8 9 6 2 29 10 16 22 27 28 23 30 1 13 11 18
VIN-3 patients

FIG. 5C

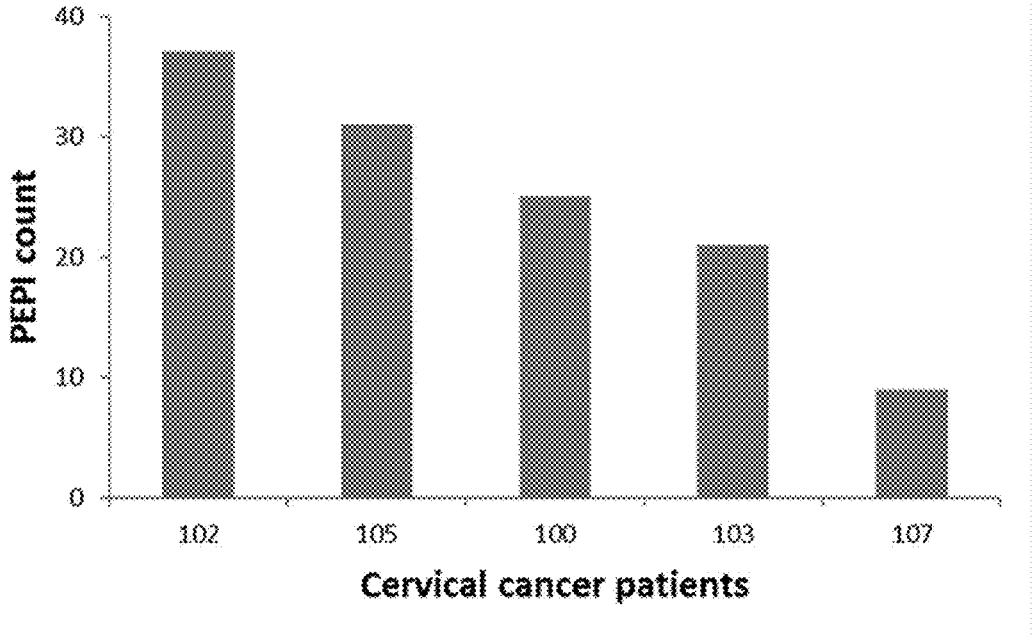
40
30
20
10
0
PEPI count
102 105 100 103 107
Cervical cancer patients

FIG. 5D

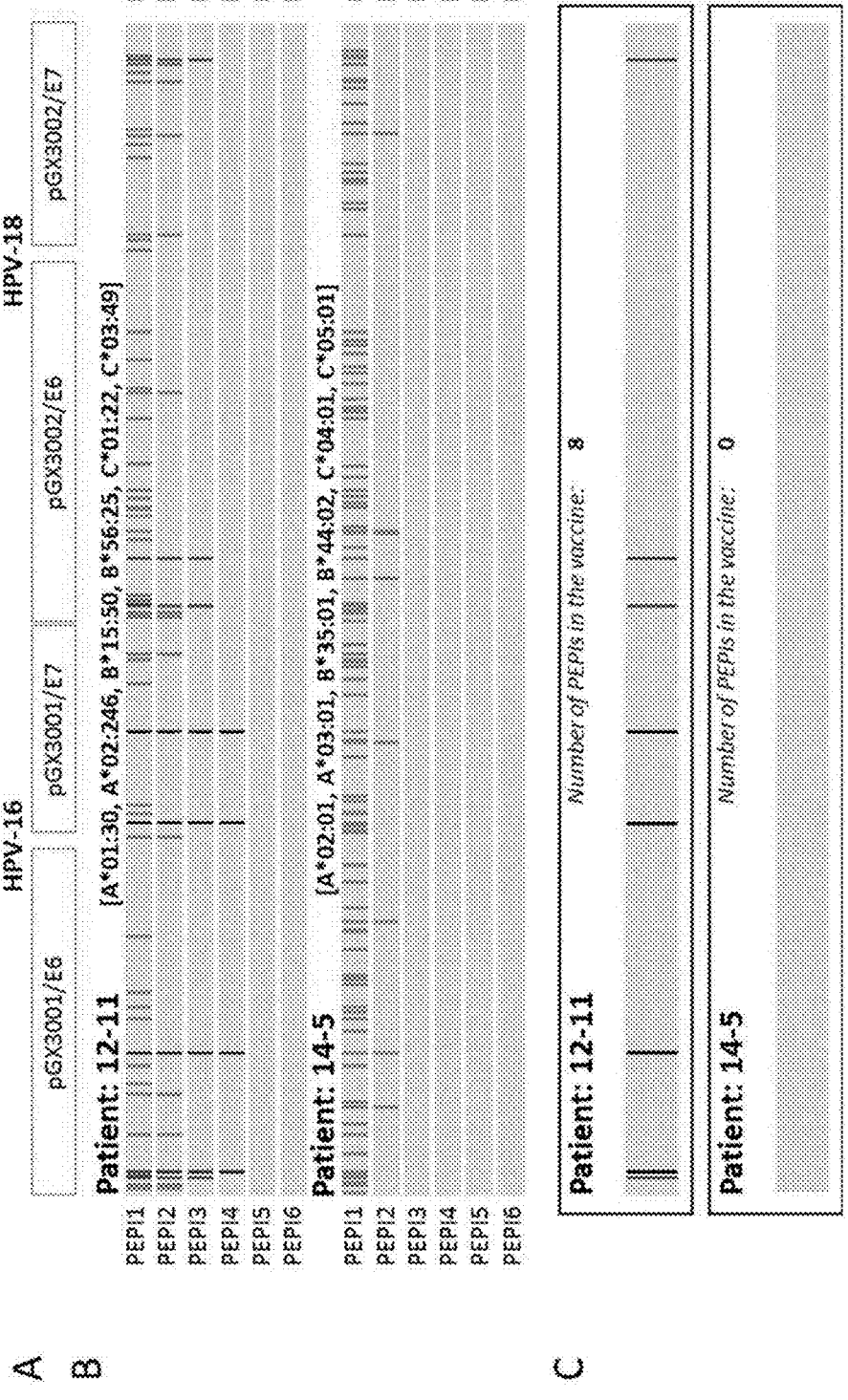
A
B
C
HPV-16
HPV-18
pGX3001/E6
pGX3001/E7
pGX3002/E6
pGX3002/E7
Patient: 12-11
[A*01:30, A*02:246, B*15:50, B*56:25, C*01:22, C*03:49]
PEPI1
PEPI2
PEPI3
PEPI4
PEPI5
PEPI6
N=54
N=21
N=8
N=4
N=0
N=0
Patient: 14-5
[A*02:01, A*03:01, B*35:01, B*44:02, C*04:01, C*05:01]
N=91
N=8
N=0
N=0
N=0
N=0
Patient: 12-11
Number of PEPIs in the vaccine: 8
Patient: 14-5
Number of PEPIs in the vaccine: 0

FIG. 6

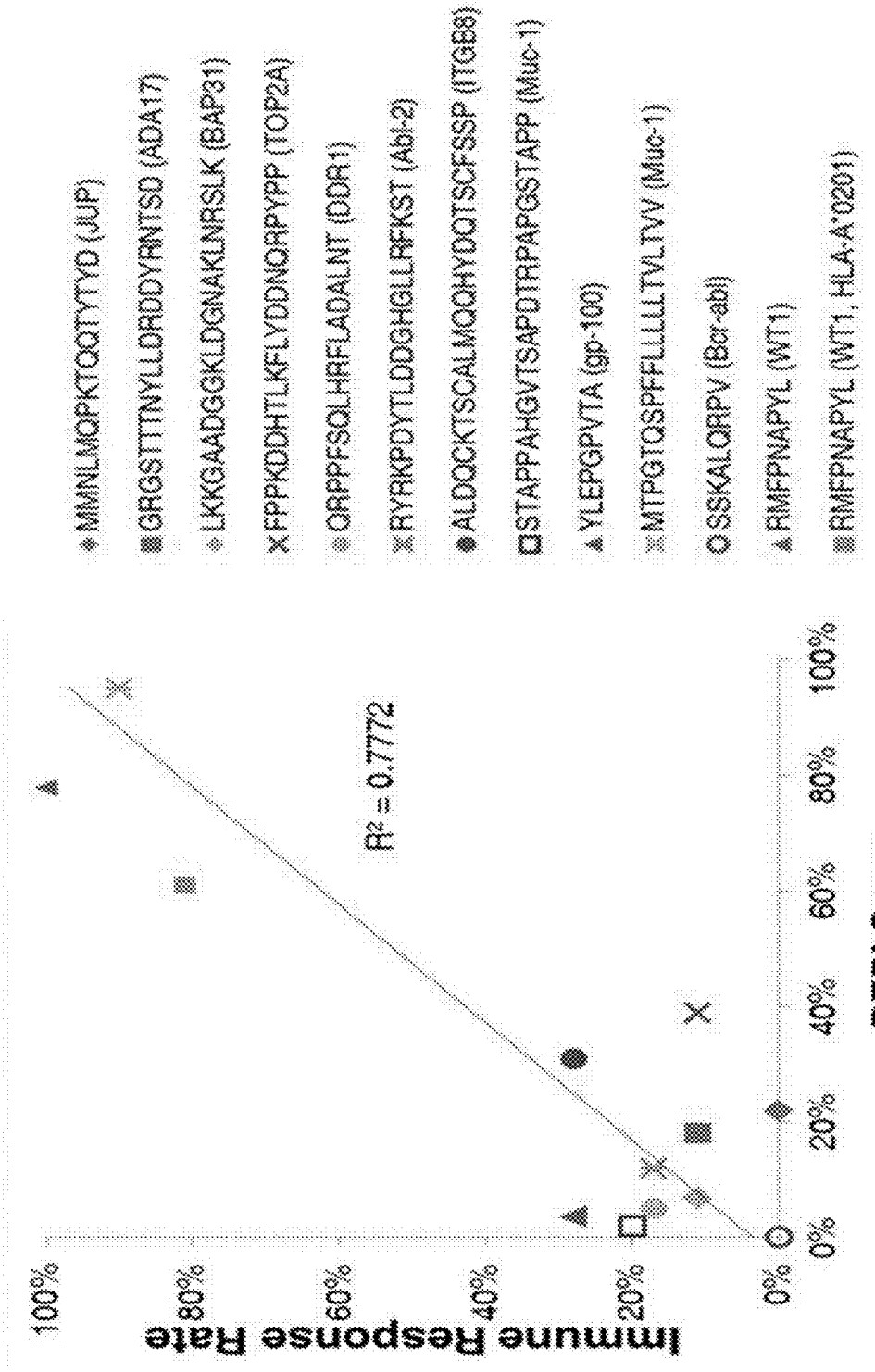
MMNLMQPKTQQTYTYD (JUP)
GRGSTTTNYLLQRDDYRNTSD (ADA17)
LKKGAADGGKLDGNAKLNRSLK (BAP31)
FPPKQDHTLKFLYDDMQRPYPP (TOP2A)
QRPPFSQLHRFLAQALNT (DDR1)
RYRKPDYTLDDGHGLLRFKST (Abl-2)
ALDQCKTSCALMQQHYDQTSCFSSP (ITGB8)
STAPPAHGVTSAPDTRPAPGSTAPP (Muc-1)
YLEPGPVTA (gp-100)
MTPGTQSPFFLLLLLTVLTVV (Muc-1)
SSKALQRPV (Bcr-abl)
RMFPNAPYL (WT1)
RMFPNAPYL (WT1, HLA-A*0201)
R² = 0.7772
Immune Response Rate
PEPI Score
0%
20%
40%
60%
80%
100%

FIG. 7

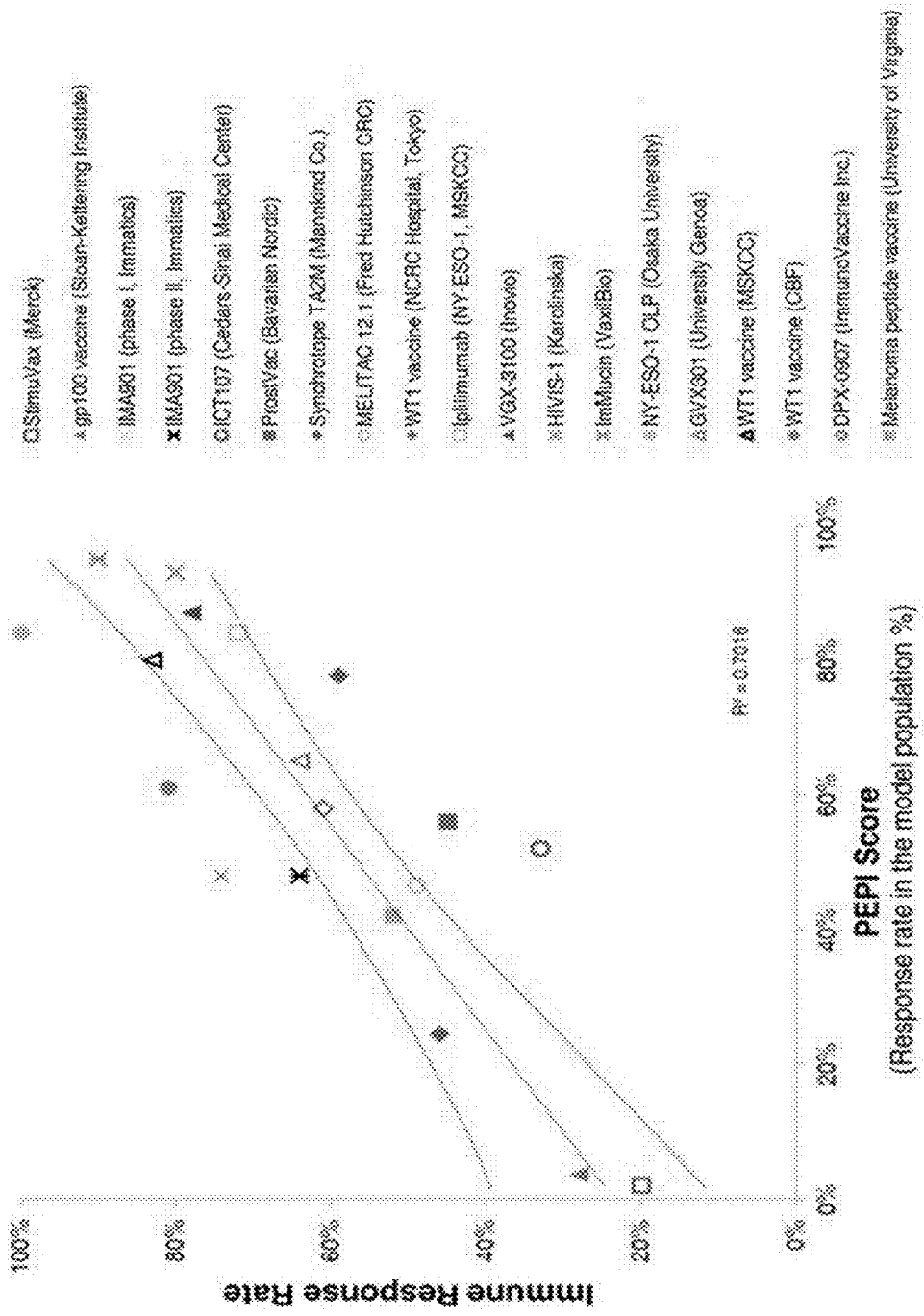
Immune Response Rate
100%
80%
60%
40%
20%
0%
0%
20%
40%
60%
80%
100%
PEPI Score
(Response rate in the model population %)
R² = 0.7018
OStimuVax (Merck)
gp100 vaccine (Sloan-Kettering Institute)
IMA901 (phase I, Immatics)
IMA901 (phase II, Immatics)
OCT107 (Cedars-Sinai Medical Center)
ProstVac (Bavarian Nordic)
Synchrotope TA2M (Mannkind Co.)
MELITAC 12.1 (Fred Hutchinson CRC)
WT1 vaccine (NCRC Hospital, Tokyo)
Ipilimumab (NY-ESO-1, MSKCC)
VGX-3100 (Inovio)
HIVIS-1 (Karolinska)
ImMucin (VaxiBio)
NY-ESO-1 CLP (Osaka University)
GVX301 (University Genoa)
WT1 vaccine (MSKCC)
WT1 vaccine (CBF)
DPX-0907 (ImmunoVaccine Inc.)
Melanoma peptide vaccine (University of Virginia)

FIG. 8

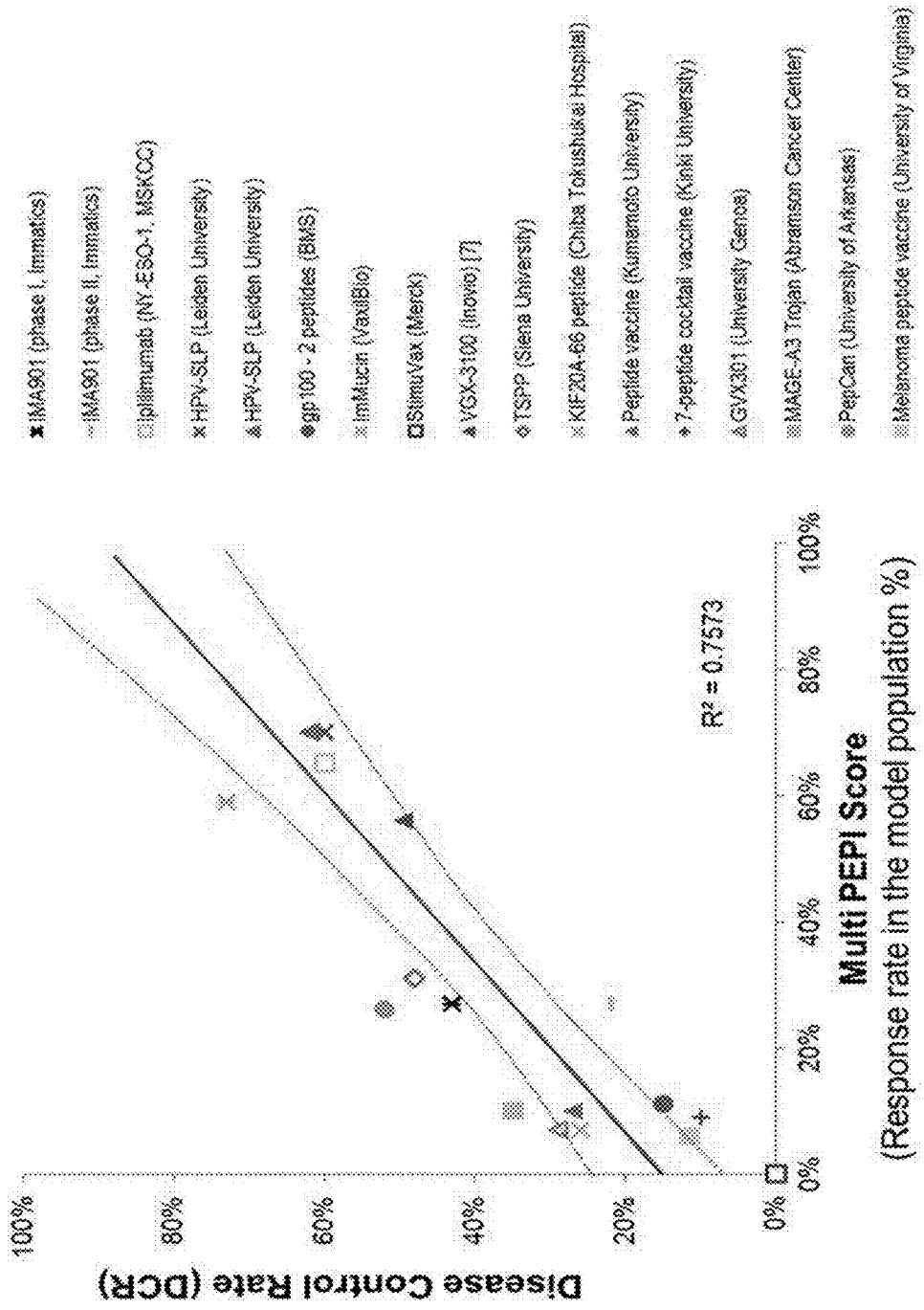
IMA901 (phase I, Immatics)
IMA901 (phase II, Immatics)
Ipilimumab (NY-ESO-1, MSKCC)
HPV-SLP (Leiden University)
HPV-SLP (Leiden University)
gp100 - 2 peptides (BMS)
ImMucin (VaxiBio)
StimuVax (Merck)
VGX-3100 (Inovio) [7]
TSPP (Siena University)
KIF20A-66 peptide (Chiba Tokushukai Hospital)
Peptide vaccine (Kumamoto University)
7-peptide cocktail vaccine (Kinki University)
GVX301 (University Genoa)
MAGE-A3 Trojan (Abramson Cancer Center)
PepCan (University of Arkansas)
Melanoma peptide vaccine (University of Virginia)
R² = 0.7573
Disease Control Rate (DCR)
100%
80%
60%
40%
20%
0%
0%
20%
40%
60%
80%
100%
Multi PEPI Score
(Response rate in the model population %)

FIG. 9

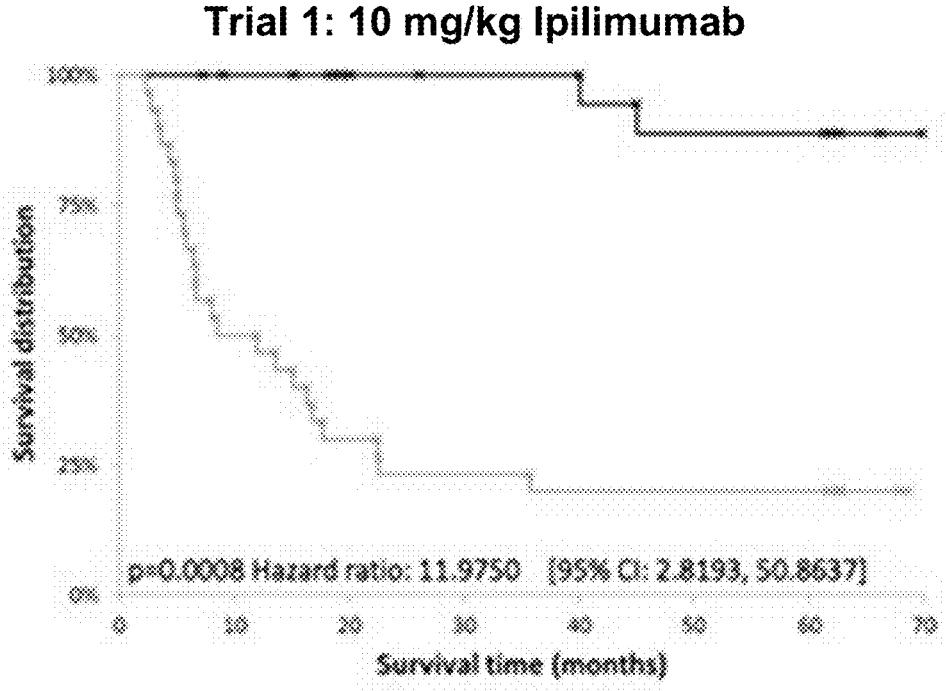

FIG. 10A

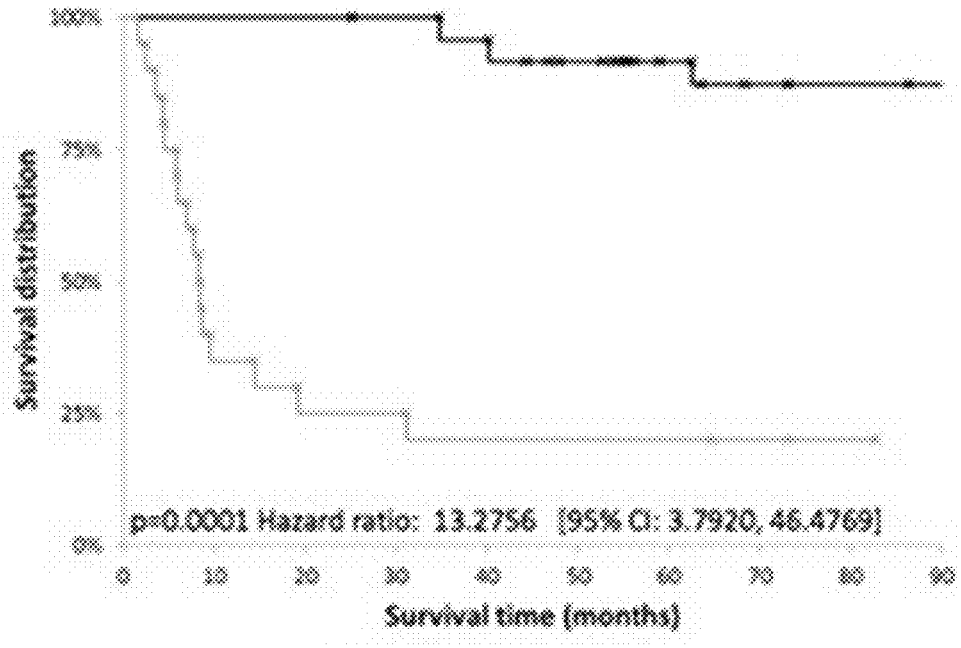

FIG. 10B

Trial 3: 3 mg/kg Ipilimumab

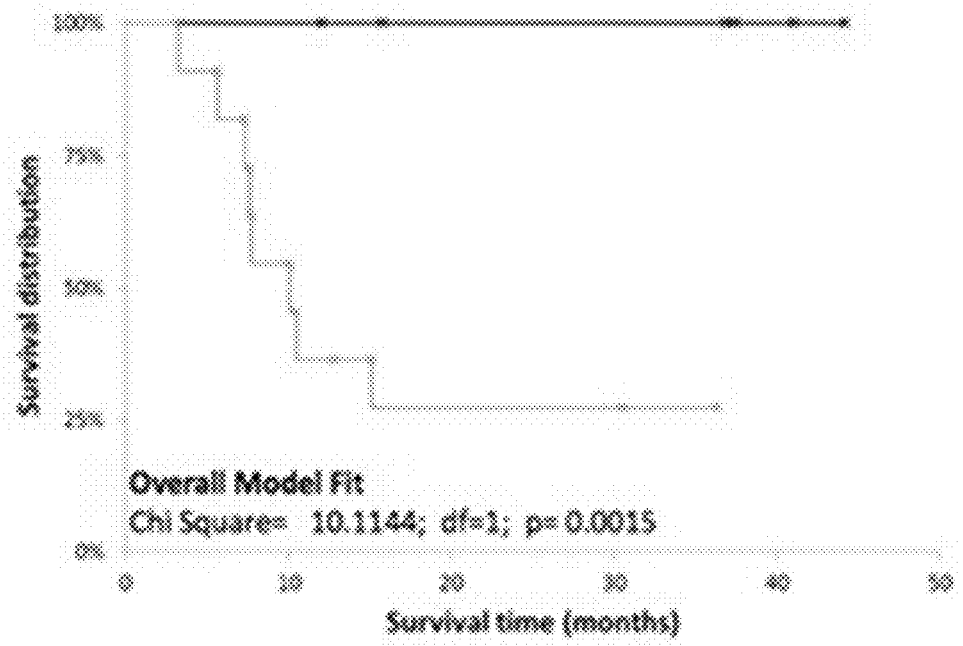

FIG. 10C

Trial 4: 3 mg/kg Ipilimumab

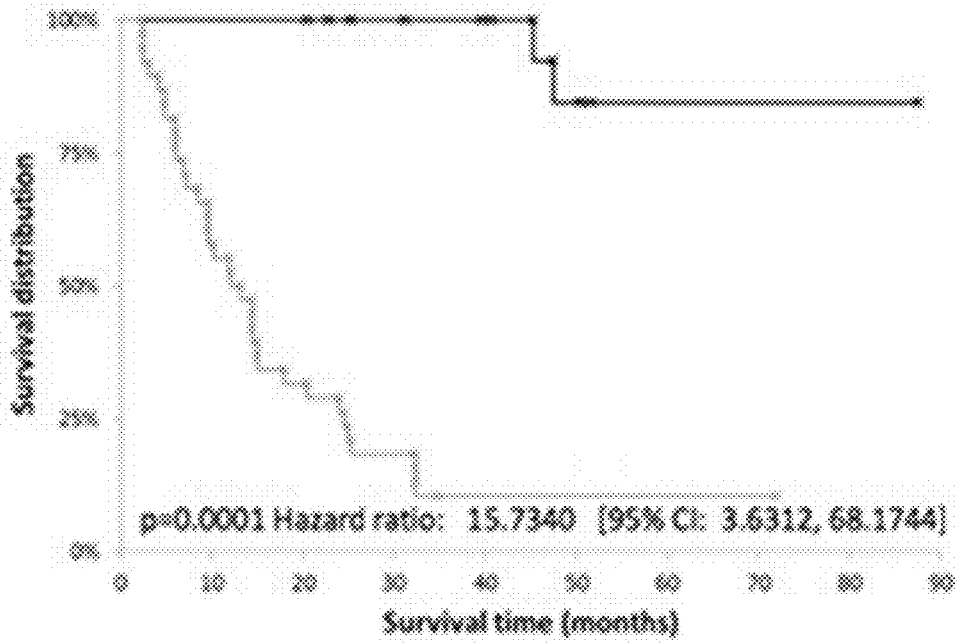

FIG. 10D

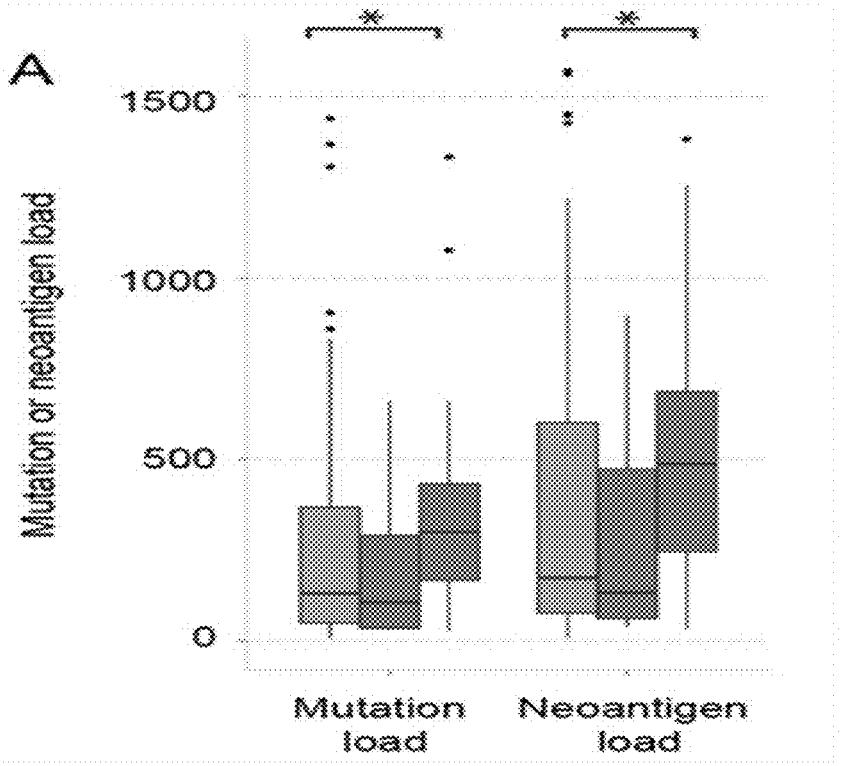

FIG. 11A

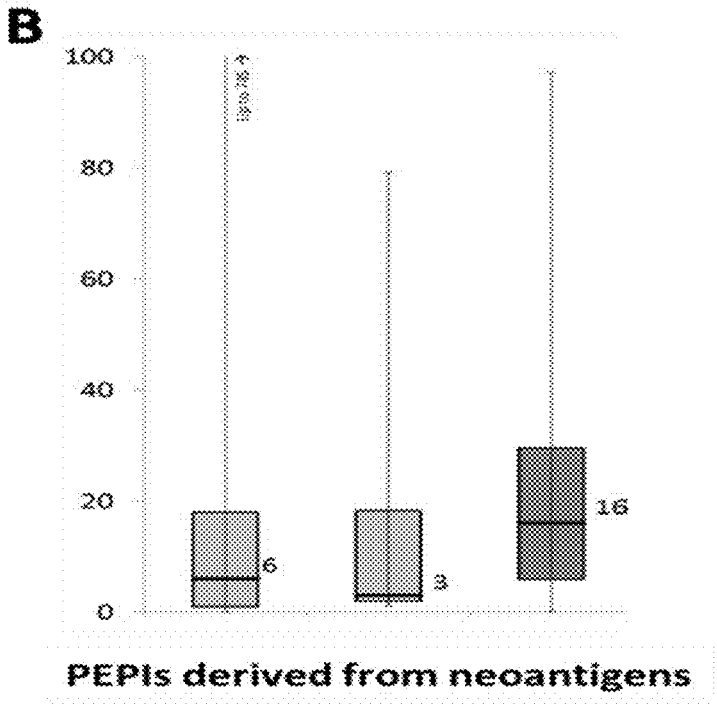

FIG. 11B

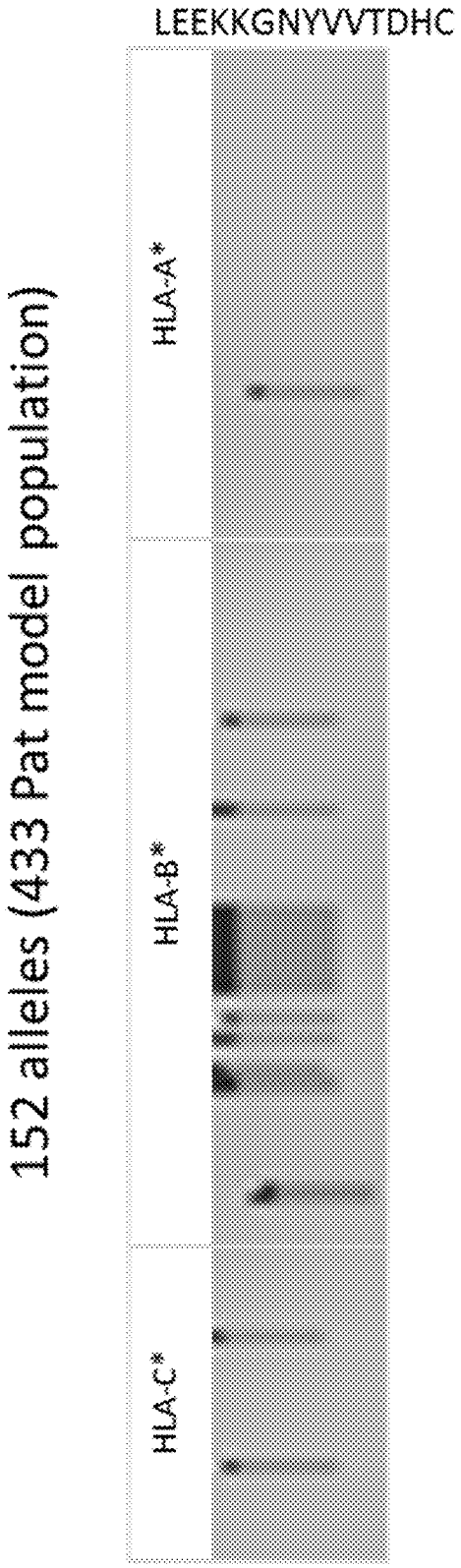
LEEKKGNYVVTDHC
152 alleles (433 Pat model population)
HLA-A*
HLA-B*
HLA-C*

FIG. 12

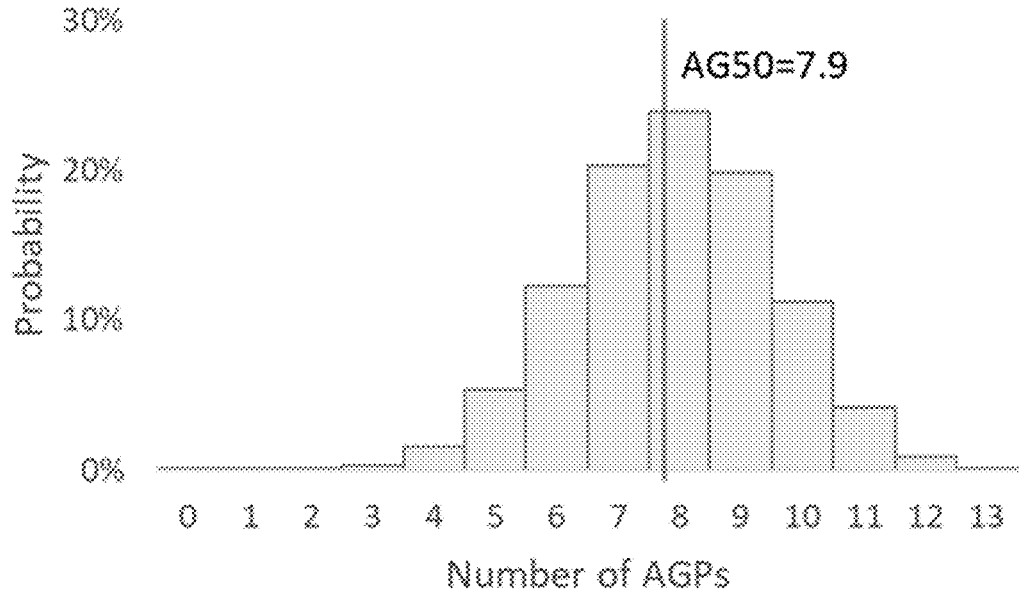

FIG. 13A

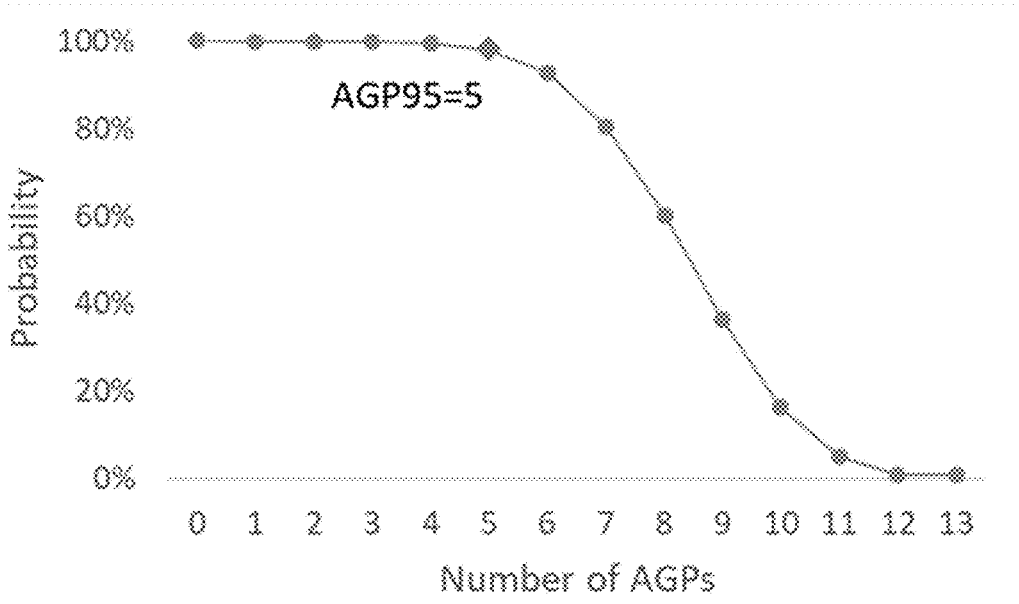

FIG. 13B

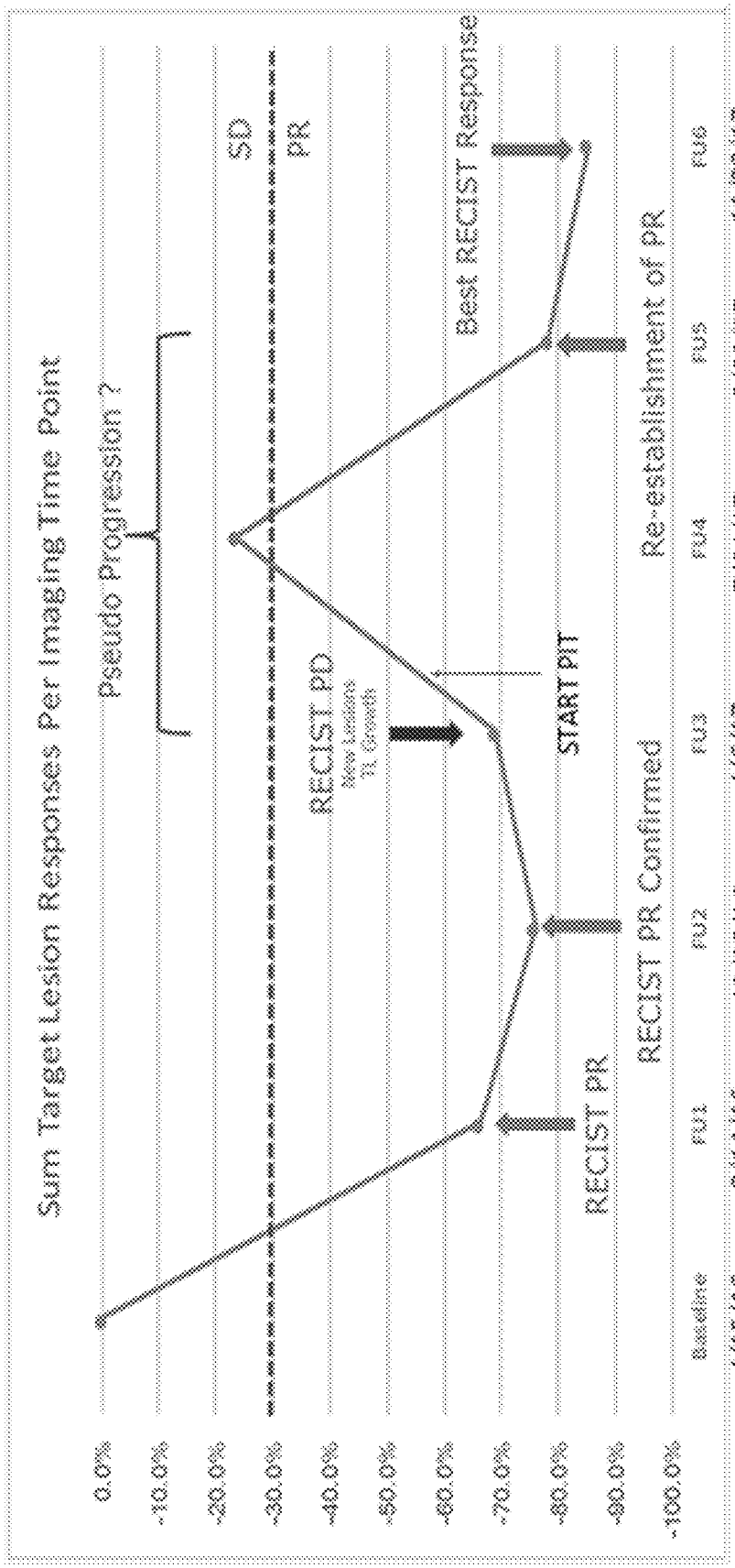
Sum Target Lesion Responses Per Imaging Time Point
Pseudo Progression ?
SD
PR
RECIST PD
New Lesion
TL Growth
Best RECIST Response
START PIT
RECIST PR
RECIST PR Confirmed
Re-establishment of PR
0.0%
-10.0%
-20.0%
-30.0%
-40.0%
-50.0%
-60.0%
-70.0%
-80.0%
-90.0%
-100.0%
Baseline
FU1
FU2
FU3
FU4
FU5
FU6
4/15/16
9/14/16
12/25/16
4/6/17
7/21/17
9/20/17
11/28/17

FIG. 14

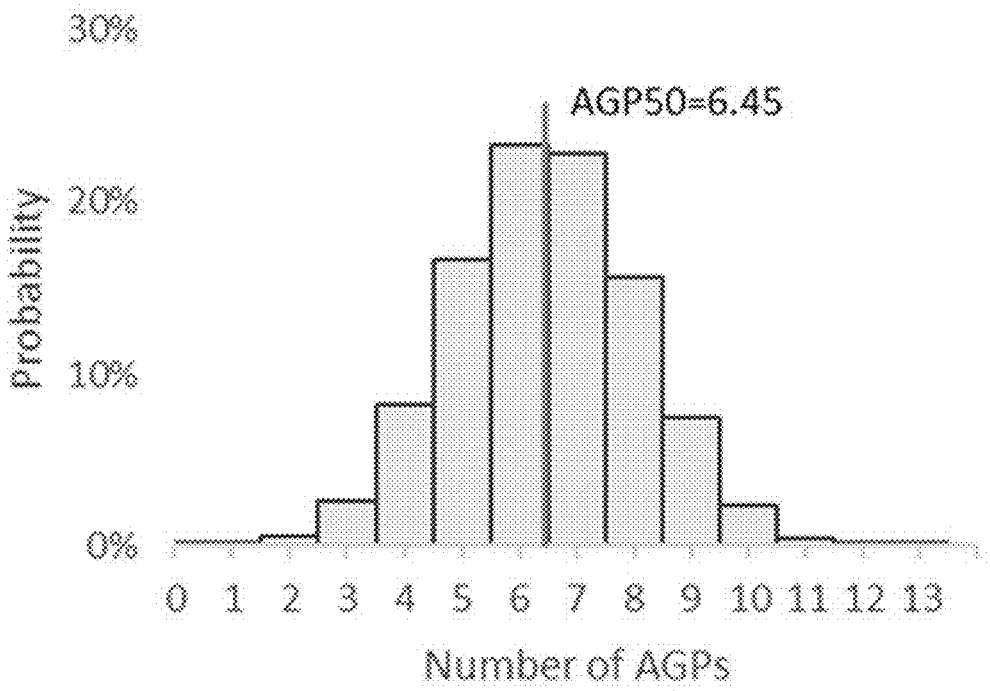

FIG. 15A

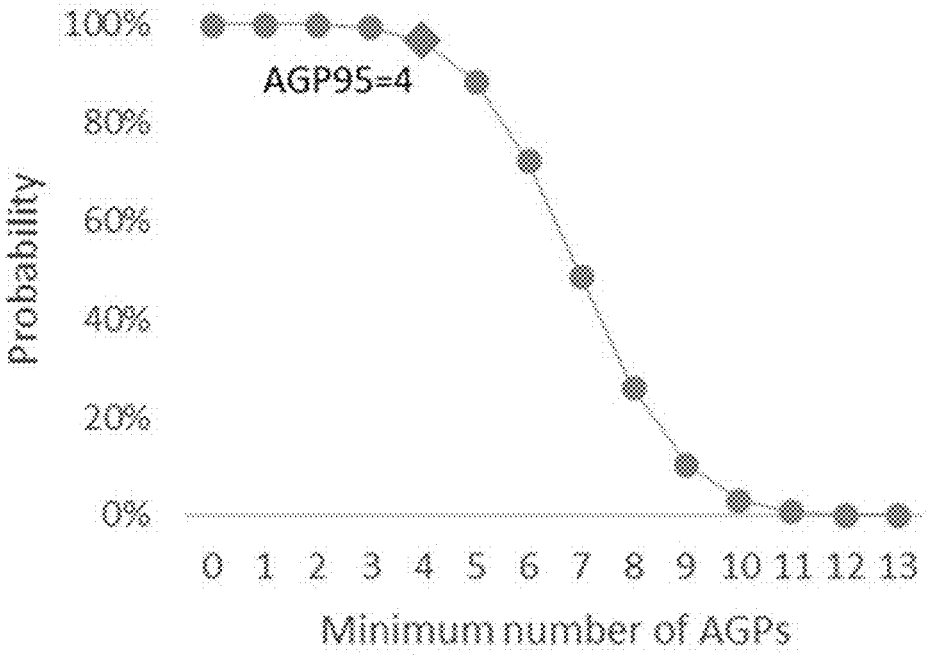

FIG. 15B

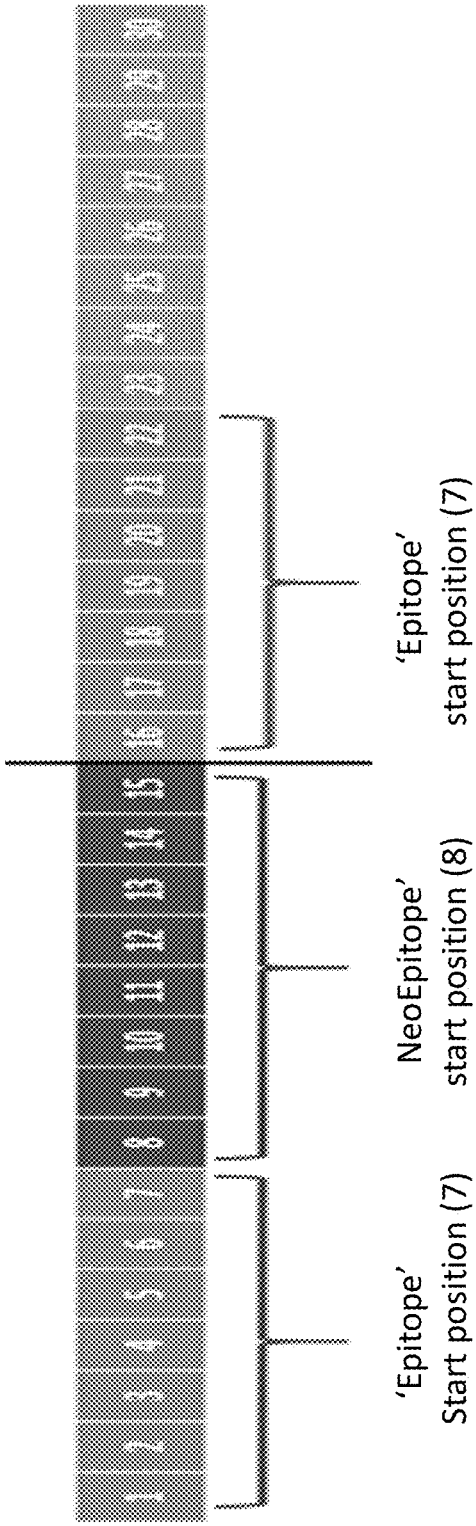
'Epitope'
Start position (7)
NeoEpitope'
start position (8)
'Epitope'
start position (7)

FIG. 16

PERSONALISED IMMUNOGENIC PEPTIDE IDENTIFICATION PLATFORM

CROSS-REFERENCE

[0001] This application claims the benefit of priority to European Application No. 17159242.1, filed on Mar. 3, 2017, European Application No. 17159243.9, filed on Mar. 3, 2017, and Great Britain Application No. 1703809.2, filed on Mar. 9, 2017, each of which is incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created May 30, 2018, is named "52895703201_SL.txt" and is 25,675 bytes in size.

FIELD

[0003] 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

[0004] 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.

[0005] 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

[0006] 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.

[0007] 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.

[0008] Accordingly, in a first aspect the disclosure provides methods of predicting whether a polypeptide or a fragment of a polypeptide is immunogenic for a specific human subject, the methods comprising the steps of

[0009] (i) determining whether the polypeptide comprises:

[0010] (a) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0011] (b) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

[0012] (ii) predicting

[0013] 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

[0014] 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).

[0015] The disclosure also provides methods of identifying a fragment of a polypeptide as immunogenic for a specific human subject, the methods comprising the steps of

[0016] (i) determining that the polypeptide comprises:

[0017] (a) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0018] (b) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

[0019] (ii) identifying said sequence as a fragment of the polypeptide that is immunogenic for the subject.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] Accordingly in a further aspect, 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:

[0026] (i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by the method above;

[0027] (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

[0028] a. comprises the fragment selected in step (i); and

[0029] b. is a T cell epitope capable of binding at least three or to the most possible HLA class II molecules of the subject;

[0030] (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);

[0031] (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;

[0032] (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

[0033] (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.

[0034] 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.

[0035] 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 of 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.

[0036] 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.

[0037] 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.

[0038] In further aspects, the disclosure provides

[0039] 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;

[0040] 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

[0041] 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.

[0042] In a further aspect 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.

[0043] 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 mol-

ecules capable of binding to the polypeptide or to one or more of the active ingredient polypeptides of the pharmaceutical composition or kit.

[0044] Disclosed herein in certain embodiments are human subject-specific pharmaceutical compositions for treatment of a disease or disorder in a specific human subject, comprising (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 (b) a pharmaceutically-acceptable adjuvant. In some embodiments, the composition comprises 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. In some embodiments, the composition comprises 3-40 different polypeptides. In some embodiments, 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. In some embodiments, the epitopes of the at least two different polypeptides are from a single antigen. In some embodiments, the epitopes of the at least two different polypeptides are from two or more different antigens. In some embodiments, the antigen is an antigen expressed by a cancer cell, a neoantigen expressed by a cancer cell, a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen. In some embodiments, the cancer cell is from the subject. In some embodiments, the antigen is selected from the antigens listed in Tables 2 to 7. In some embodiments, the at least two 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. In some embodiments, 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. In some embodiments, two of the at least two polypeptides are arranged end to end or overlapping in a joined polypeptide. In some embodiments, the composition comprises two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other. In some embodiments, 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). In some embodiments, the at least two polypeptides do not comprise any amino acid sequences that (i) correspond to a fragment of a human polypeptide expressed in healthy cells; or (ii) correspond to a fragment of a human polypeptide expressed in healthy cells and is a T cell epitope capable of binding to at least two HLA class I molecules of the subject. In some embodiments, the composition further comprises a pharmaceutically acceptable diluent, carrier, preservative, or combination thereof. In some embodiments, the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

[0045] Disclosed herein in certain embodiments are kits 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 (ii) a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof. In some embodiments, the kit 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. In some embodiments, the kit further comprises a package insert.

[0046] Disclosed herein in certain embodiments are human subject-specific pharmaceutical compositions 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. In some embodiments, 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.

[0047] Disclosed herein in certain embodiments are human subject-specific pharmaceutical compositions 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. In some embodiments, 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. In some embodiments, the

composition comprises 2-40 different polypeptides. In some embodiments, 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. In some embodiments, the epitopes of the first and second regions are from a single antigen. In some embodiments, the epitopes of the first and second regions are from two or more different antigens. In some embodiments, the antigen is an antigen expressed by a cancer cell, a neoantigen expressed by a cancer cell, a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen. In some embodiments, the cancer cell is from the subject. In some embodiments, the antigen is selected from the antigens listed in Tables 2 to 7. In some embodiments, the polypeptides have been screened to eliminate substantially all neoepitopes that span a junction between the 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 (iii) meets both requirements (i) and (ii). In some embodiments, 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 (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. In some embodiments, the composition further comprises a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof. In some embodiments, the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof.

[0048] Disclosed herein in certain embodiments are methods of preparing a human subject-specific pharmaceutical composition for use in a method of treatment of a specific human subject, the method comprising:

[0049] (i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by

[0050] a) determining whether the fragment comprises:

[0051] 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

[0052] 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

[0053] 3) or meets both requirements (1) and (2); and

[0054] b) identifying the sequence as a fragment of the polypeptide that is immunogenic for the subject;

[0055] (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

[0056] (iii) preparing a subject-specific pharmaceutical composition having as active ingredients one or more polypeptides that together have all of the amino acid sequences selected in the preceding steps.

In some embodiments, the method further comprises 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. In some embodiments, the method further comprises, 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. In some embodiments, the method further comprises prior to the preparing step selecting a longer 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. In some embodiments, 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 joined polypeptide. In some embodiments, 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 (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). In some embodiments, 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. In some embodiments, the method further comprises determining HLA class I genotype and HLA class II genotype from a biological sample of the subject prior to step (i). In some embodiments, the biological sample is obtained from the subject. In some embodiments, the determining HLA class I genotype and HLA class II genotype is performed by sequence based typing (SBT) methods. In some embodiments, 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. In some embodiments, the biological sample is blood, serum, plasma, saliva, buccal swab, urine, expiration, cell, or tissue. In some embodiments, the biological sample is saliva or a buccal swab.

[0057] Disclosed herein in certain embodiments are methods 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. In some embodiments, 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. In some embodiments, the composition comprises 2-40 different polypeptides. In some embodiments, 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. In some embodiments, 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. In some embodiments, 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. In some embodiments, the one or more antigen is a neoantigen expressed by a cancer cell, a cancer-associated antigen, or a tumor-associated antigen. In some embodiments, the one or more antigen is selected from the antigens listed in Table 2. In some embodiments, 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. In some embodiments, 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. In some embodiments, the composition comprises at least two different polypeptides and two of the polypeptides are arranged end to end or overlapping in a joined polypeptide. In some embodiments, the composition comprises two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other. In some embodiments, 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). In some embodiments, 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. In some embodiments, the composition further comprises a pharmaceutically acceptable adjuvant, diluent, carrier, preservative, or combination thereof. In some embodiments, the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof. In some embodiments, the method further comprises administering a chemotherapeutic agent, a targeted therapy, radiation therapy, a checkpoint inhibitor, another immunotherapy, or combination thereof.

[0058] Disclosed herein in some embodiments are human subject-specific pharmaceutical compositions 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. In some embodiments, 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, 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. In some embodiments, the composition comprises 2-40 different polypeptides. In some embodiments, 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. In some embodiments, the composition comprises at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are from a single antigen. In some embodiments, the composition comprises at least two different polypeptides, wherein the epitopes of the at least two different polypeptides are from two or more different antigens. In some embodiments, the antigen is an antigen expressed by a cancer cell, a neoantigen expressed by a cancer cell, a cancer-associated antigen, a tumor-associated antigen, or an antigen expressed by a target pathogenic organism, an antigen expressed by a virus, an antigen expressed by a bacterium, an antigen expressed by a fungus, an antigen associated with an autoimmune disorder, or is an allergen. In some embodiments, the cancer cell is from the subject. In some embodiments, the antigen is selected from the antigens listed in Tables 2 to 7. In some embodiments, the composition comprises at least two different polypeptides, wherein two of the polypeptides are arranged end to end or overlapping in a joined polypeptide. In some embodiments, the adjuvant is selected from the group consisting of Montanide ISA-51, QS-21, GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete), Freunds adjuvant (incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, oil emulsions, dinitrophenol, diphtheria toxin (DT), and combinations thereof. In some embodiments, the composition comprises at least two different polypeptides, wherein two of the at least two polypeptides are arranged end to end or overlapping in a joined polypeptide. In some embodiments, the composition comprises two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different epitopes from each other. In some embodiments, 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). In some embodiments, the at least two polypeptides do not comprise any amino acid sequences that (i) correspond to a fragment of a human polypeptide expressed in healthy cells; or (ii) correspond to a fragment of a human polypeptide expressed in healthy cells and is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

[0059] Disclosed herein in certain embodiments are kits comprising: 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; and 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. In some embodiments, 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.

[0060] 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.

[0061] The present disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or is stated to be expressly avoided. As used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a peptide" includes two or more such peptides.

[0062] Section headings are used herein for convenience only and are not to be construed as limiting in any way.

DESCRIPTION OF THE FIGURES

[0063] FIG. **1**—ROC curve of HLA restricted PEPI biomarkers.

[0064] FIG. **2**—ROC curve of ≥1 PEPI3+ Test for the determination of the diagnostic accuracy.

[0065] FIGS. **3**A-B—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. FIG. **3**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. FIG. **3**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.

[0066] FIGS. **4**A-B—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. FIG. **4**A: HLA class II restricted PEPI4+s. 67% OPA between PEPI4+ and CD4+ T-cell responses ($p=0.002$). FIG. **4**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.

[0067] FIGS. **5**A-D—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 (FIGS. **5**A and **5**B) and HLA class II restricted PEPI3 counts (FIGS. **5**C and **5**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.

[0068] FIG. **6**—The multiple HLA class I binding peptides that define the HPV vaccine specific T cell response set of 2 patients. Panel 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. Panel 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 1^{st} 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). Panel C: The DNA vaccine specific PEPI3+ set of two patients characterizes their vaccine specific T cell responses.

[0069] FIG. **7**—Correlation between the ≥1 PEPI3+ Score and CTL response rates of peptide targets determined in clinical trials. FIG. **7** discloses SEQ ID NOS 1-4, 6, 5 and 7-13, respectively, in order of appearance.

[0070] FIG. **8**—Correlation between the ≥1 PEPI3+ Score and the clinical Immune Response Rate (IRR) of immunotherapy vaccines. Dashed lines: 95% confidence band.

[0071] FIG. **9**—Correlation between the ≥2 PEPI3+ Score and Disease Control Rate (DCR) of immunotherapy vaccines. Dashed lines: 95% confidence band.

[0072] FIGS. **10**A-D—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. FIG. **10**A: Trial 1: 18 HLA responders and 30 HLA non responders; FIG. **10**B: Trial 2: 24 HLA responders and 20 HLA non responders; FIG. **10**C: Trial 3: 6 HLA responders and 11 HLA non responders; FIG. **10**D: Trial 4: 13 HLA responders and 38 HLA non responders

[0073] FIGS. **11**A-B—Multiple HLA binding peptides in mutational neoantigens. FIG. **11**A: Correlation of mutational load, neoantigen load (neoantigens are neoepitopes according to van Allen) and FIG. **11**B: Correlation of PEPI3+ load and clinical benefit (min-Q1-median-Q3-max).

[0074] FIG. **12**—HLA map of the Rindopepimut on the HLA alleles of the subjects in the Model Population. FIG. **12** discloses SEQ ID NO: 87.

[0075] FIGS. **13**A-B—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).

[0076] 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.

[0077] FIGS. **15**A-B—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).

[0078] 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

[0079] SEQ ID NOs: 1 to 13 set forth the additional peptide sequences described in Table 17.

[0080] SEQ ID NOs: 14-26 set forth personalised vaccine peptides designed for patient XYZ described in Table 26.

[0081] SEQ ID NOs: 27-38 set forth personalised vaccine peptides designed for patient ABC described in Table 29.

[0082] SEQ ID NOs: 39-86 set forth further 9 mer T cell epitopes described in Table 33.

DETAILED DESCRIPTION

HLA Genotypes

[0083] 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.

[0084] 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.

[0085] 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

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] "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.

[0091] "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.

[0092] "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.

[0093] "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.

[0094] "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.

[0095] "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.

[0096] 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.

[0097] 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

[0098] (i) determining whether the polypeptide comprises:

[0099] 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

[0100] 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

[0101] (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.

[0102] 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

	WEB ADDRESS
EPITOPE PREDICTION TOOLS	
BIMAS, NIH	www-bimas.cit.nih.gov/molbio/hla_bind/
PPAPROC, Tubingen Univ.	
MHCPred, Edward Jenner Inst. of Vaccine Res.	
EpiJen, Edward Jenner Inst. of Vaccine Res.	http://www.ddg-pharmfac.net/epijen/EpiJen/EpiJen.htm
NetMHC, Center for Biological Sequence Analysis	http://www.cbs.dtu.dk/services/NetMHC/
SVMHC, Tubingen Univ.	http://abi.inf.uni-tuebingen.de/Services/SVMHC/
SYFPEITHI, Biomedical Informatics, Heidelberg	http://www.syfpeithi.de/bin/MHCServer.dll/EpitopePrediction.htm
ETK EPITOOLKIT, Tubingen Univ.	http://etk.informatik.uni-tuebingen.de/epipred/
PREDEP, Hebrew Univ. Jerusalem	http://margalit.huji.ac.il/Teppred/mhc-bind/index.html
RANKPEP, MIF Bioinformatics	http://bio.dfci.harvard.edu/RANKPEP/
IEDB, Immune Epitope Database	http://tools.immuneepitope.org/main/html/tcell_tools.html
EPITOPE DATABASES	
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/

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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

[0107] 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.

[0108] 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.

[0109] In some cases the polypeptide is, or the polypeptide consists of all or part of an antigen that is, expressed by a pathogenic organism (for example, a bacteria or a parasite), a virus, or a cancer cell, that is associated with an autoimmune disorder or response or a disease-associated cell, or that is an allergen, or an ingredient of a medicine or pharmaceutical composition such as a vaccine or immunotherapy composition. In some cases the method of the disclosure comprises an initial step of identifying or selecting a suitable polypeptide, for example a polypeptide as further described below.

[0110] 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 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.

[0111] The polypeptide or antigen may be a cancer- or tumor-associated antigen (TAA). TAAs are proteins expressed in cancer or tumor cells. The cancer or tumour cell may be present in a sample obtained from 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 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/).

[0112] In some cases the polypeptide or antigen is not expressed or is minimally expressed in normal healthy cells or tissues, but is expressed (in those cells or tissues) in a high proportion of (with a high frequency in) subjects having a particular disease or condition, such as a type of cancer or a cancer derived from a particular cell type or tissue, for example breast cancer, ovarian cancer or melanoma. A further example is colorectal cancer. Other non-limiting cancer examples include non-melanoma skin, lung, prostate, kidney, bladder, stomach, liver, cervix uteri, oesophagus, non-Hodgkin lymphoma, leukemia, pancreas, corpus uteri, lip, oral cavity, thyroid, brain, nervous system, gallbladder, larynx, pharynx, myeloma, nasopharynx, Hodgkin lymphoma, testis and Kaposi sarcoma. Alternatively, the polypeptide may be expressed at low levels in normal healthy cells, but at high levels (overexpressed) in diseased (e.g. cancer) cells or in subjects having the disease or condition. In some cases the polypeptide is expressed in, or expressed at a high level relative to normal healthy cells or subjects in, at least 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of such individuals, or of a subject-matched human subpopulation. 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.

[0113] 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.

[0114] 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.

[0115] 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).

[0116] 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.

[0117] 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).

[0118] 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.

[0119] 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.

[0120] In other cases the polypeptide may be a target polypeptide antigen of a pharmaceutical, vaccine or immunotherapy composition. A polypeptide is a target polypeptide antigen if the composition is intended or designed to induce an immune response (e.g. a cytotoxic T cell response) that targets or is directed at the polypeptide. A target polypeptide antigen is typically a polypeptide that is expressed by a pathogenic organism, a virus or a diseased cell such as a cancer cell. A target polypeptide antigens may be a TAA or a CTA.

[0121] Presently, >200 clinical trials are investigating cancer vaccines with tumor antigens.

[0122] The polypeptide may be an allergen that enters the body of an individual through, for example, the skin, lung or oral routes.

[0123] Non-limiting examples of suitable polypeptides include those listed in one or more of Tables 2 to 7.

[0124] Genetic sequences may be obtained from the sequencing of biological materials. Sequencing can be done by any suitable method that determines DNA and/or RNA and/or amino acid sequences. The disclosure utilizes both the HLA genotypes and amino acid sequences. However, methods to identify HLA genotype from genetic sequences of an individual and methods of obtaining amino acid sequences derived from DNA or RNA sequence data are not the subject of the disclosure.

TABLE 2

LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS.

		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***	BAH	O14514.1
BAL	P19835.1	BALF2	P03227.1	BALF4	P03188.1	BALF5	P03198.1
BARF1	P03228.1	BBRF1	P03213.1	BCAN	Q96GW7.1	BCAP31	P51572.1
BCL-2	P10415.1	BCL2L1	Q07817.1	BCL6	P41182.1	BCL9	O00512.1
BCR	P11274.1	BCRF1	P03180.1	BDLF3	P03224.1	BGLF4	P13288.1
BHLF1	P03181.1	BHRF1	P03182.1	BILF1	P03208.1	BILF2	P03218.1
BIN1	O00499.1	BING-4	O15213.1	BIRC7	Q96CA5.1	BLLF1	P03200.1
BLLF2	P03199.1	BMI1	P35226.1	BMLF1	Q04360.1	BMPR1B	O00238.1
BMRF1	P03191.1	BNLF2a	P0C739.1	BNLF2b	Q8AZJ3.1	BNRF1	P03179.1
BRAF1	P15056.1	BRD4	O60885.1	**BRDT**	**Q58F21.1***	BRI3BP	Q8WY22.1
BRINP1	O60477.1	BRLF1	P03209.1	BTBD2	Q9BX70.1	BUB1B	O60566.1
BVRF2	P03234.1	BXLF1	P03177.1	BZLF1	P03206.1	**C15orf60**	**Q7Z4M0.1***
CA 12-5	Q8WXI7.1	CA 19-9	Q969X2.1	CA195	Q5TG92.1	CA9	Q16790.1
CABYR	**O75952.1***	CADM4	Q8NFZ8.1	**CAGE1**	**Q8CT20.1***	CALCA	P01258.1

TABLE 2-continued

LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS.

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**	**PODMU7.1***
CT46	**Q86X24.1***	**CT47**	**Q5JQC4.1***	**CT47B1**	**P0C2P7.1***	**CTAGE2**	**Q96RT6.1***
cTAGE5	**O15320.1***	**CTCFL**	**Q8NI51.1***	CTDSP2	O14595.1	CTGF	P29279.1
CTLA4	P16410.1	**CTNNA2**	**P26232.1***	CTNNB1	P35222.1	CTNND1	O60716.1
CTSH	P09668.1	**CTSP1**	**A0RZH4.1***	CTTN	Q14247.1	CXCR4	P61073.1
CXorf48	**Q8WUE5.1***	**CXorf61**	**Q5H943.1***	Cyclin-E	P24864.1	CYP1B1	Q16678.1
CypB	P23284.1	CYR61	O00622.1	CS1	P28290.1	**CSAG1**	**Q6PB30.1***
CSDE1	O75534.1	CSF1	P09603.1	CSF1R	P07333.1	CSF3R	Q99062.1
CSK	P41240.1	CSK23	Q8NEV1.1	DAPK3	O43293.1	DAZ1	Q9NQZ3.1
DBPC	Q9Y2T7.1	**DCAF12**	**Q5T6F0.1***	DCT	P40126.1	DCUN1D1	Q96GG9.1
DCUN1D3	Q8IWE4.1	DDR1	Q08345.1	DDX3X	O00571.1	DDX6	P26196.1
DEDD	O75618.1	DEK	P35659.1	DENR	O43583.1	DEPDC1	Q5TB30.1
DFNA5	O60443.1	DGAT2	Q96PD7.1	DHFR	P00374.1	DKK1	O94907.1
DKK3	Q9UBP4.1	**DKKL1**	**Q9UK85.1***	DLEU1	O43261.1	DMBT1	Q9UGM3.1
DMRT1	**Q9Y5R6.1***	**DNAJB8**	**Q8NHS0.1***	DNAJC8	O75937.1	DNMT3A	Q9Y6K1.1
DPPA2	**Q727J5.1***	DR4	O00220.1	DR5	O14763.1	**DRG1**	**Q9Y295.1***
DSCR8	Q96T75.1	E2F3	O00716.1	E2F6	O75461.1	E2F8	A0AVK6.1
EBNA1	P03211.1	EBNA2	P12978.1	EBNA3	P12977.1	EBNA4	P03203.1
EBNA6	P03204.1	EBNA-LP	Q8AZK7.1	E-cadherin	P12830.1	ECT2	Q9H8V3.1
ECTL2	Q008S8.1	**EDAG**	**Q9BXL5.1***	EEF2	P13639.1	EFNA1	P20827.1
EES	O43281.1	EFTUD2	Q15029.1	EGFL7	Q9UHF1.1	EGFR	p00533.1
EI24	O14681.1	EIF4EBP1	Q13541.1	ELF3	P78545.1	ELF4	Q99607.1
ELOVL4	**Q9GZR5.1***	EMP1	P54849.1	ENAH	Q8N8S7.1	Endosialin	Q9HCU0.1
ENO1	P06733.1	ENO2	P09104.1	ENO3	P13929.1	ENTPD5	O75356.1
EpCAM	P16422.1	EPHA2	P29317.1	EPHA3	P29320.1	EPHB2	P29323.1
EPHB4	P54760.1	EPHB6	O15197.1	EPS8	Q12929.1	ERBB3	P21860.1
ERBB4	Q15303.1	EREG	O14944.1	ERG	P11308.1	ERVK-18	O42043.1
ERVK-19	O71037.1	ESR1	P03372.1	ETAA1	Q9NY74.1	ETS1	P14921.1
ETS2	P15036.1	ETV1	P50549.1	ETV5	P41161.1	ETV6	P41212.1
EVI5	O60447.1	EWSR1	Q01844.1	EYA2	O00167.1	EZH2	Q15910.1
FABP7	O15540.1	**FAM133A**	**Q8N9E0.1***	FAM13A	O94988.1	**FAM46D**	**Q8NEK8.1***
FAM58BP	P0C7Q3.1	FANCG	O15287.1	**FATE1**	**Q969F0.1***	**FBXO39**	**Q8N4B4.1***
FBXW11	Q9UKB1.1	FCHSD2	O94868.1	FER	P16591.1	FES	P07332.1
FEV	Q99581.1	FGF10	O15520.1	FGF23	Q9GZV9.1	FGF3	P11487.1
FGF4	P08620.1	FGF5	P12034.1	FGFR1	P11362.1	FGFR2	P21802.1
FGFR3	P22607.1	FGFR4	P22455.1	FGR	P09769.1	FLI1	Q01543.1
FLT3	P36888.1	FMNL1	O95466.1	FMOD	Q06828.1	**FMR1NB**	**Q8N0W7.1***
FN1	P02751.1	Fn14	Q9NP84.1	FNIP2	Q9P278.1	FOLR1	P15328.1
FOS	P01100.1	FosB	P53539.1	FOSL1	P15407.1	FOXM1	Q08050.1
FOXO1	Q12778.1	FOXO3	O43524.1	FRAT1	Q92837.1	FRMD3	A2A2Y4.1
FSIP1	Q8NA03.1	FSIP2	Q5CZC0.1	FSTL3	O95633.1	**FTHL17**	**Q9BXU8.1***
FUNDC2	Q9BWH2.1	FUS	P35637.1	FUT1	P19526.1	FUT3	P21217.1
FYN	P06241.1	GAB2	Q9UQC2.1	GADD45G	O95257.1	**GAGE-1**	**Q13065.1**
GAGE12B/C/D/E	**A1L429.1**	**GAGE12F**	**P0CL80.1**	**GAGE12G**	**P0CL81. 1**	**GAGE12H**	**A6NDE8.1**
GAGE12I	**P0CL82.1**	**GAGE12J**	**A6NER3.1**	**GAGE-2**	**Q6NT46.1**	**GAGE-3**	**Q13067.1**
GAGE-4	**Q13068.1**	**GAGE-5**	**Q13069.1**	**GAGE-6**	**Q13070.1**	**GAGE-7**	**O76087.1**

TABLE 2-continued

LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS.

GAGE-8	**Q9UEU5.1**	GALGT2	Q00973.1	GAS7	O60861.1	GASZ	Q8WWH4.1
GATA-3	P23771.1	GBU4-5	Q587J7.1	GCDFP-15	P12273.1	GFAP	P14136.1
GFI1	Q99684.1	Ghrelin	Q9UBU3.1	GHSR	Q92847.1	GIPC1	O14908.1
GITR	Q9Y5U5.1	GKAP1	Q5VSY0.1	GLI1	P08151.1	Glypican-3	P51654.1
GML	Q99445.1	GNA11	P29992.1	GNAQ	P50148.1	GNB2L1	P63244.1
GOLGA5	Q8TBA6.1	gp100	P40967.1	gp75	P17643.1	Gp96	P14625.1
GPAT2	**Q6NUI2.1***	**GPATCH2**	**Q9NW75.1***	GPC-3	P51654.1	GPNMB	Q14956.1
GPR143	P51810.1	GPR89A	B7ZAQ6.1	GRB2	P62993.1	GRP78	P11021.1
GUCY1A3	Q02108.1	H3F3A	P84243.1	**HAGE**	**Q9NXZ2.1***	hANP	P01160.1
HBEGF	Q99075.1	hCG-beta	P01233.1	HDAC1	Q13547.1	HDAC2	Q92769.1
HDAC3	O15379.1	HDAC4	P56524.1	HDAC5	Q9UQL6.1	HDAC6	Q9UBN7.1
HDAC7	Q8WUI4.1	HDAC8	Q9BY41.1	HDAC9	Q9UKV0.1	HEATR1	Q9H583.1
Hepsin	P05981.1	Her2/neu	P04626.1	HERC2	O95714.1	HERV-K104	P61576.1
HEXB	P07686.1	HEXIM1	O94992.1	HGRG8	Q9Y5A9.1	HIPK2	Q9H2X6.1
HJURP	Q8NCD3.1	HMGB1	P09429.1	HMOX1	P09601.1	HNRPL	P14866.1
HOM-TES-85	**Q9P127.1***	**HORMAD1**	**Q86X24.1***	**HORMAD2**	**Q8N7B1.1***	HPSE	Q9Y251.1
HPV16 E6	P03126.1	HPV16 E7	P03129.1	HPV18 E6	P06463.1	HPV18 E7	P06788.1
HRAS	P01112.1	HSD17B13	Q7Z5P4.1	HSP105	Q92598.1	HSP60	P10809.1
HSPA1A	P08107.1	**HSPB9**	**Q9BQS6.1***	HST-2	P10767.1	HT001	Q2TB18.1
hTERT	O14746.1	HUS1	O60921.1	ICAM-1	P05362.1	IDH1	O75874.1
IDO1	P14902.1	IER3	P46695.1	IGF1R	P08069.1	**IGFS11**	**Q5DX21.1***
IL13RA2	**Q14627.1***	**IMP-3**	**Q9NV31.1***	ING3	Q9NXR8.1	INPPL1	O15357.1
INTS6	Q9UL03.1	IRF4	Q15306.1	IRS4	O14654.1	ITGA5	P08648.1
ITGB8	P26012.1	ITPA	Q9BY32.1	ITPR2	Q14571.1	JAK2	O60674.1
JAK3	P52333.1	**JARID1B**	**Q9UGL1.1***	JAZF1	Q86VZ6.1	JNK1	P45983.1
JNK2	P45984.1	JNK3	P53779.1	JTB	O76095.1	JUN	P05412.1
JUP	P14923.1	K19	P08727.1	KAAG1	Q9UBP8.1	Kallikrein 14	Q9P0G3.1
Kallikrein 4	Q9Y5K2.1	KAT6A	Q92794.1	KDM1A	O60341.1	KDM5A	P29375.1
KIAA0100	**Q14667.1***	KIAA0336	Q8IWJ2.1	KIAA1199	Q8WUJ3.1	KIAA1641	A6QL64.1
KIF11	P52732.1	KIF1B	O60333.1	KIF20A	O95235.1	KIT	P10721.1
KLF4	O43474.1	KLHL41	O60662.1	KLK10	O43240.1	KMT2D	O14686.1
KOC1	O00425.1	K-ras	P01116.1	KRIT1	O00522.1	KW-12	P62913.1
KW-2	Q96RS0.1	KW-5 (SEBD4)	Q9H0Z9.1	KW-7	O75475.1	L1CAM	P32004.1
L53	Q96EL3.1	L6	Q9BTT4.1	LAG3	P18627.1	**Lage-1**	**O75638.1***
LATS1	O95835.1	LATS2	Q9NRM7.1	LCMT2	O60294.1	LCP1	P13796.1
LDHC	**P07864.1***	LDLR	P01130.1	**LEMD1**	**Q68G75.1***	Lengsin	Q5TDP6.1
LETMD1	Q6P1Q0.1	LGALS3BP	Q08380.1	LGALS8	O00214.1	LIN7A	O14910.1
LIPI	**Q6XZB0.1***	LIV-1	Q13433.1	LLGL1	Q15334.1	LMO1	P25800.1
LMO2	P25791.1	LMP1	P03230.1	LMP2	P13285.1	**LOC647107**	**Q8TAI5.1***
LOXL2	Q9Y4K0.1	LRP1	Q07954.1	LRRN2	O75325.1	LTF	P02788.1
LTK	P29376.1	LZTS1	Q9Y250.1	**LY6K**	**Q17RY6.1***	LYN	P07948.1
LYPD6B	**Q8NI32.1***	MAEA	Q7L5Y9.1	**MAEL**	**Q96JY0.1***	MAF	O75444.1
MAFF	Q9ULX9.1	MAFG	O15525.1	MAFK	O60675.1	**MAGE-A1**	**P43355.1***
MAGE-A10	**P43363.1***	**MAGE-A11**	**P43364.1***	**MAGE-A12**	**P43365.1***	**MAGE-A2**	**P43356.1***
MAGE-A2B	**Q6P448.1***	**MAGE-A3**	**P43357.1***	**MAGE-A4**	**P43358.1***	**MAGE-A5**	**P43359.1***
MAGE-A6	**P43360.1***	**MAGE-A8**	**P43361.1***	**MAGE-A9**	**P43362.1***	**MAGE-B1**	**P43366.1***
MAGE-B2	**O15479.1***	**MAGE-B3**	**O15480.1***	**MAGE-B4**	**O15481.1***	**MAGE-B5**	**Q9BZ81.1***
MAGE-B6	**Q8N7X4.1***	**MAGE-C1**	**O60732.1***	**MAGE-C2**	**Q9UBF1.1***	**MAGE-C3**	**Q8TD91.1***
mammaglobin-A	Q13296.1	MANF	P55145.1	MAP2K2	P36507.1	MAP2K7	O14733.1
MAP3K7	O43318.1	MAP4K5	Q9Y4K4.1	MART1	Q16655.1	MART-2	Q5VTY9.1
MAS1	P04201.1	MC1R	Q01726.1	**MCAK**	**Q99661.1***	MCF2	P10911.1
MCF2L	O15068.1	MCL1	Q07820.1	MCTS1	Q9ULC4.1	MCSP	Q6UVK1.1
MDK	P21741.1	MDM2	Q00987.1	MDM4	O15151.1	ME1	P48163.1
ME491	P08962.1	MECOM	Q03112.1	MELK	Q14680.1	MEN1	O00255.1
MERTK	Q12866.1	MET	P08581.1	MFGE8	Q08431.1	MFHAS1	Q9Y4C4.1
MFI2	P08582.1	MGAT5	Q09328.1	Midkine	P21741.1	MIF	P14174.1
MKI67	P46013.1	MLH1	P40692.1	MLL	Q03164.1	MLLT1	Q03111.1
MLLT10	P55197.1	MLLT11	Q13015.1	MLLT3	P42568.1	MLLT4	P55196.1
MLLT6	P55198.1	MMP14	P50281.1	MMP2	P08253.1	MMP7	P09237.1
MMP9	P14780.1	MOB3B	Q86TA1.1	**MORC1**	**Q86VD1.1***	**MPHOSPH1**	**Q96Q89.1***
MPL	P40238.1	MRAS	O14807.1	MRP1	P33527.1	MRP3	O15438.1
MRPL28	Q13084.1	MRPL30	Q8TCC3.1	MRPS11	P82912.1	MSLN	Q13421.1
MTA1	Q13330.1	MTA2	O94776.1	MTA3	Q9BTC8.1	MTCP1	P56278.1
MTSS1	O43312.1	MUC-1	P15941.1	MUC-2	Q02817.1	MUC-3	Q02505.1
MUC-4	Q99102.1	MUC-5AC	P98088.1	MUC-6	Q6W4X9.1	MUM1	Q2TAK8.1
MUM2	Q9Y5R8.1	MYB	P10242.1	MYC	P01106.1	MYCL	P12524.1
MYCLP1	P12525.1	MYCN	P04198.1	MYD88	Q99836.1	MYEOV	Q96EZ4.1
MYO1B	O43795.1	**NA88-A**	**P0C5K6.1***	NAE1	Q13564.1	Napsin-A	O96009.1
NAT6	Q93015.1	NBAS	A2RRP1.1	NBPF12	Q5TAG4.1	NCOA4	Q13772.1
NDC80	O14777.1	NDUFC2	O95298.1	Nectin-4	Q96NY8.1	NEK2	P51955.1
NEMF	O60524.1	NENF	Q9UMX5.1	NEURL1	O76050.1	NFIB	O00712.1
NFKB2	Q00653.1	NF-X1	Q12986.1	NFYC	Q13952.1	NGAL	P80188.1
NGEP	Q6IWH7.1	NKG2D-L1	Q9BZM6.1	NKG2D-L2	Q9BZM5.1	NKG2D-L3	Q9BZM4.1
NKG2D-L4	Q8TD07.1	NKX3.1	Q99801.1	NLGN4X	Q8N0W4.1	**NLRP4**	**Q96MN2.1***
NNMT	P40261.1	**NOL4**	**O94818.1***	NOTCH2	Q04721.1	NOTCH3	Q9UM47.1

TABLE 2-continued

LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS.

NOTCH4	Q99466.1	NOV	P48745.1	NPM1	P06748.1	**NR6A1**	**Q15406.1***
N-RAS	P01111.1	NRCAM	Q92823.1	NRP1	O14786.1	NSE1	Q96KN4.1
NSE2	Q96KN1.1	NTRK1	P04629.1	NUAK1	O60285.1	NUGGC	Q68CJ6.1
NXF2	**Q9GZY0.1***	**NXF2B**	**Q5JRM6.1***	NY-BR-1	Q9BXX3.1	NYD-TSPG	Q9BWV7.1
NY-ESO-1	**P78358.1***	NY-MEL-1	P57729.1	OCA2	Q04671.1	**ODF1**	**Q14990.1***
ODF2	**Q5BJF6.1***	**ODF3**	**Q96PU9.1***	**ODF4**	**Q2M2E3.1***	OGG1	O15527.1
OGT	O15294.1	**OIP5**	**O43482.1***	OS9	Q13438.1	**OTOA**	**Q05BM7.1***
OX40	P43489.1	OX40L	P23510.1	P53	P04637.1	P56-LCK	P06239.1
PA2G4	Q9UQ80.1	**PAGE1**	**O75459.1***	**PAGE2**	**Q7Z2X2.1***	**PAGE2B**	**Q5JRK9.1***
PAGE3	**Q5JUK9.1***	**PAGE4**	**O60829.1***	**PAGE5**	**Q96GU1.1***	PAK2	Q13177.1
PANO1	I0J062.1	PAP	Q06141.1	PAPOLG	Q9BWT3.1	PARK2	O60260.1
PARK7	Q99497.1	PARP12	Q9H0J9.1	**PASD1**	**Q8IV76.1***	PAX3	P23760.1
PAX5	Q02548.1	PBF	P00751.1	**PBK**	**Q96KB5.1***	PBX1	P40424.1
PCDC1	Q15116.1	PCM1	Q15154.1	PCNXL2	A6NKB5.1	PDGFB	P01127.1
PDGFRA	P16234.1	**PEPP2**	**Q9HAU0.1***	PGF	P49763.1	PGK1	P00558.1
PHLDA3	Q9Y5J5.1	PHLPP1	O60346.1	PIAS1	O75925.1	PIAS2	O75928.1
PIK3CA	P42336.1	PIK3CD	O00329.1	PIK3R2	O00459.1	PIM1	P11309.1
PIM2	Q9P1W9.1	PIM3	Q86V86.1	PIR	O00625.1	**PIWIL1**	**Q96J94.1***
PIWIL2	**Q8TC59.1***	PIWIL3	Q7Z3Z3.1	PIWIL4	Q7Z3Z4.1	PKN3	Q6P5Z2.1
PLA2G16	P53816.1	**PLAC1**	**Q9HBJ0.1***	PLAG1	Q6DJT9.1	PLEKHG5	O94827.1
PLK3	Q9H4B4.1	PLS3	P13797.1	PLVAP	Q9BX97.1	PLXNB1	O43157.1
PLXNB2	O15031.1	PML	P29590.1	PML-RARA	Q96QH2.1	**POTEA**	**Q6S8J7.1***
POTEB	**Q6S5H4.1***	**POTEC**	**B2RU33.1***	**POTED**	**Q86YR6.1***	**POTEE**	**Q6S8J3.1***
POTEG	**Q6S5H5.1***	**POTEH**	**Q6S545.1***	PP2A	P63151.1	PPAPDC1B	Q8NEB5.1
PPFIA1	Q13136.1	PPIG	Q13427.1	PPP2R1B	P30154.1	**PRAME**	**P78395.1***
PRDX5	P30044.1	PRKAA1	Q13131.1	PRKCI	P41743.1	**PRM1**	**P04553.1***
PRM2	**P04554.1***	PRMT3	O60678.1	PRMT6	Q96LA8.1	PDL1	Q9NZQ7.1
PROM1	O43490.1	**PRSS54**	**Q6PEW0.1***	**PRSS55**	**Q6UWB4.1***	PRTN3	P24158.1
PRUNE	Q86TP1.1	PRUNE2	Q8WUY3.1	PSA	P07288.1	PSCA	D3DWI6.1
PSMA	Q04609.1	PSMD10	O75832.1	PSGR	Q9H255.1	PSP-94	Q1L6U9.1
PTEN	P60484.1	PTH-rP	P12272.1	PTK6	Q13882.1	**PTPN20A**	**Q4JDL3.1***
PTPRK	Q15262.1	PTPRZ	P23471.1	PTTG-1	O95997.1	PTTG2	Q9NZH5.1
PTTG3	Q9NZH4.1	PXDNL	A1KZ92.1	RAB11FIP3	O75154.1	RAB8A	P61006.1
RAD1	O60671.1	RAD17	O75943.1	RAD51C	O43502.1	RAF1	P04049.1
RAGE-1	Q9UQ07.1	RAP1A	P62834.1	RARA	P10276.1	RASSF10	A6NK89.1
RB1	P06400.1	RBL2	Q08999.1	**RBM46**	**Q8TBY0.1***	RBP4	P02753.1
RCAS1	O00559.1	RCVRN	P35243.1	RECQL4	O94761.1	RET	P07949.1
RGS22	**Q8NE09.1***	RGS5	O15539.1	RHAMM	O75330.1	RhoC	P08134.1
RHOXF2	Q9BQY4.1	RL31	P62888.1	RNASET2	O00584.1	RNF43	Q68DV7.1
RNF8	O76064.1	RON	Q04912.1	**ROPN1A**	**Q9HAT0.1***	ROR1	Q01973.1
RPA1	O95602.1	RPL10A	P62906.1	RPL7A	P62424.1	RPS2	P15880.1
RPS6KA5	O75582.1	RPSA	P08865.1	**RQCD1**	**Q92600.1***	RRAS2	P62070.1
RSL1D1	O76021.1	RTKN	Q9BST9.1	RUNX1	Q01196.1	RUNX2	Q13950.1
RYK	P34925.1	**SAGE1**	**Q9NXZ1.1***	SART2	Q9UL01.1	SART3	Q15020.1
SASH1	O94885.1	sCLU	P10909.1	SCRN1	Q12765.1	SDCBP	O00560.1
SDF-1	P48061.1	SDHD	O14521.1	SEC31A	O94979.1	SEC63	Q9UGP8.1
Semaphorin 4D	Q92854.1	**SEMG1**	**P04279.1***	SFN	P31947.1	SH2B2	O14492.1
SH2D1B	O14796.1	SH3BP1	Q9Y3L3.1	SHB	Q15464.1	SHC3	Q92529.1
SIRT2	Q8IXJ6.1	SIVA1	O15304.1	SKI	P12755.1	SLBP	A9UHW6.1
SLC22A10	Q63ZE4.1	SLC25A47	Q6QOC1.1	SLC35A4	Q96G79.1	SLC45A3	Q96JT2.1
SLC4A1AP	Q9BWU0.1	**SLCO6A1**	**Q86UG4.1***	SLITRK6	Q9H5Y7.1	Sm23	P27701.1
SMAD5	Q99717.1	SMAD6	O43541.1	SMO	Q99835.1	Smt3B	P61956.1
SNRPD1	P62314.1	SOS1	Q07889.1	SOX-2	P48431.1	SOX-6	P35712.1
SOX-11	P35716 .1	**SPA17**	**Q15506.1***	**SPACA3**	**Q8IXA5.1***	**SPAG1**	**Q07617.1***
SPAG17	**Q6Q759.1***	**SPAG4**	**Q9NPE6.1***	**SPAG6**	**O75602.1***	**SPAG8**	**Q99932.1***
SPAG9	**O60271.1***	**SPANXA1**	**Q9NS26.1***	**SPANXB**	**Q9NS25.1***	**SPANXC**	**Q9NY87.1***
SPANXD	**Q9BXN6.1***	**SPANXE**	**Q8TAD1.1***	**SPANXN1**	**Q5VSR9.1***	**SPANXN2**	**Q5MJ10.1***
SPANXN3	**Q5MJ09.1***	**SPANXN4**	**Q5MJ08.1***	**SPANXN5**	**Q5MJ07.1***	**SPATA19**	**Q7Z5L4.1***
SPEF2	**Q9C093.1***	SPI1	P17947.1	**SPINLW1**	**O95925.1***	**SPO11**	**Q9Y5K1.1***
SRC	P12931.1	SSPN	Q14714.1	**SSX-1**	**Q16384.1***	**SSX-2**	**Q16385.1***
SSX-3	**Q99909.1***	**SSX-4**	**O60224.1***	**SSX-5**	**O60225.1***	**SSX-6**	**Q7RTT6.1***
SSX-7	**Q7RTT5.1***	**SSX-9**	**Q7RTT3.1***	ST18	O60284.1	STAT1	P42224.1
STEAP1	Q9UHE8.1	STK11	Q15831.1	STK25	O00506.1	STK3	Q13188.1
STN	Q9H668.1	SUPT7L	O94864.1	Survivin	O15392.1	SUV39H1	O43463.1
SYCE1	**Q8N0S2.1**	**SYCP1**	**Q15431.1**	SYCP3	Q8IZU3.1	SYT	Q15532.1
TA-4	Q96RI8.1	TACC1	O75410.1	TAF1B	Q53T94.1	TAF4	O00268.1
TAF7L	**Q5H9L4.1***	**TAG-1**	**Q02246.1***	TAL1	P17542.1	TAL2	Q16559.1
TAPBP	O15533.1	TATI	P00995.1	TAX1BP3	O14907.1	TBC1D3	Q8IZP1.1
TBP-1	P17980.1	TCL1A	P56279.1	TCL1B	O95988.1	TDHP	Q9BT92.1
TDRD1	**Q9BXT4.1***	**TDRD4**	**Q9BXT8.1***	**TDRD6**	**O60522.1***	**TEKT5**	**Q96M29.1***
TEX101	**Q9BY14.1***	**TEX14**	**Q8IWB6.1***	**TEX15**	**Q9BXT5.1***	**TEX38**	**Q6PEX7.1***
TF	P02787.1	**TFDP3**	**Q5H9I0.1***	TFE3	P19532.1	TGFBR1	P36897.1
TGFBR2	P37173.1	**THEG**	**Q9P2T0.1***	TIE2	Q02763.1	TIPRL	O75663.1
TLR2	O60603.1	**TMEFF1**	**Q8IYR6.1***	**TMEFF2**	**Q9UIK5.1***	**TMEM108**	**Q6UXF1.1***
TMEM127	O75204.1	**TMPRSS12**	**Q86WS5.1***	TNC	P24821.1	TNFRSF17	Q02223.1

TABLE 2-continued

LIST OF NAMED TUMOUR ANTIGENS WITH CORRESPONDING ACCESSION NUMBERS.

TNFSF15	O95150.1	TNK2	Q07912.1	TOMM34	Q15785.1	TOP2A	P11388.1
TOP2B	Q02880.1	TOR3A	Q9H497.1	TP73	O15350.1	TPA1	8N543.1
TPGS2	Q68CL5.1	TPI1	P60174.1	TPL2	P41279.1	TPM4	P67936.1
TPO	P40225.1	**TPPP2**	**P59282.1***	TPR	P12270.1	**TPTE**	**P56180.1***
TRAF5	O00463.1	**TRAG-3**	**Q9Y5P2.1***	TRGC2	P03986.1	TRIM24	O15164.1
TRIM37	O94972.1	TRIM68	Q6AZZ1.1	TRPM8	Q7Z2W7.1	**TSGA10**	**Q9BZW7.1***
TSP50	**Q9UI38.1***	TSPAN6	O43657.1	**TSPY1**	**Q01534.1***	**TSPY2**	**A6NKD2.1***
TSPY3	**Q6B019.1***	TSPYL1	Q9H0U9.1	**TSSK6**	**Q9BXA6.1***	TTC23	Q5W5X9.1
TTK	**P33981.1***	**TULP2**	**O00295.1***	TUSC2	O75896.1	TWEAK	O43508.1
TXNIP	Q9H3M7.1	TYMS	P04818.1	TYR	P14679.1	U2 snRNP B	P08579.1
U2AF1	Q01081.1	UBD	O15205.1	UBE2A	P49459.1	UBE2C	O00762.1
UBE2V1	Q13404.1	UBE4B	O95155.1	UBR5	O95071.1	UBXD5	Q5T124.1
UFL1	O94874.1	URI1	O94763.1	URLC10	Q17RY6.1	UROC1	Q96N76.1
USP2	O75604.1	USP4	Q13107.1	VAV1	P15498.1	VCX3A	Q9NNX9.1
VEGFR1	P17948.1	VEGFR2	P35968.1	VHL	P40337.1	VIM	P08670.1
VWA5A	O00534.1	WHSC2	Q9H3P2.1	WISP1	O95388.1	WNK2	Q9Y3S1.1
WNT10B	O00744.1	WNT3	P56703.1	WNT-5a	P41221.1	WT1	P19544.1
WWP1	Q9H0M0.1	**XAGE-1**	**Q9HD64.1***	**XAGE-2**	**Q96GT9.1***	**XAGE-3**	**Q8WTP9.1***
XAGE-4	**Q8WWM0.1**	**XAGE-5**	**Q8WWM1.1***	XBP1	P17861.1	XPO1	O14980.1
XRCC3	O43542.1	YB-1	P67809.1	YEATS4	O95619.1	YES1	P07947.1
YKL-40	P36222.1	ZBTB7A	O95365.1	ZBTB7C	A1YPR0.1	ZEB1	P37275.1
ZFYVE19	Q96K21.1	**ZNF165**	**P49910.1***	ZNF185	O15231.1	ZNF217	O75362.1
ZNF320	A2RRD8.1	ZNF395	Q9H8N7.1	**ZNF645**	**Q8N7E2.1***	ZUBR1	Q5T4S7.1
ZW10	O43264.1	ZWINT	O95229.1				

CTAs = bold and *

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	45617.1	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	138948.1
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

TABLE 4-continued

LIST OF ACCESSION NUMBERS FOR BACTERIAL ANTIGENS FROM IEDB

I6Y3P5.1	Q2FYP2.1	P9WG41.1	P96890.1	O06625.1	I6X654.1	Q8YIE1.1	P9WQ81.1
I6XWA1.1	P11311.1	O53900.1	P9WIR7.1	P9WQB1.1	B8ZUC6.1	O06802.1	P9WMK1.1
P9WG37.1	Q2FWC4.1	Q2GGE3.1	O33347.1	P9WJ09.1	P9WJ11.1	P9WF23.1	O69703.1
I6X4K0.1	B2RM93.1	P71888.1	P9WFW3.1	P9WPV1.1	P9WPU7.1	P9WPV3.1	P9WPU5.1
O50391.1	P9WID7.1	P9WPC3.1	P96901.1	O84848.1	Q2FUX4.1	A0A0M1YNY3.1	P49944.1
P9WPQ9.1	Q45010.1	Q2FZK7.1	P9WMN3.1	P9WPQ1.1	Q45013.1	O53666.1	Q5NEH1.1
P9WHR5.1	P9WIE5.1	Q5NEQ3.1	P9WNF3.1	F2QBN0.1	B8ZTB7.1	P0C922.1	P9WMJ9.1
Q5NGW2.1	P01556.1	Q8DMZ4.1	P33768.1	Q2FUY2.1	Q5NG56.1	X8CE55.1	Q5NGE4.1
P94973.1	O06827.1	P96872.1	I6X9Y7.1	I6XFZ8.1	O50442.1	O53697.1	O53978.1
P95137.1	P95144.1	O53519.1	Q79FZ8.1	P9WJF5.1	P71629.1	P9WJS3.1	P9WPB7.1
Q7D9T1.1	P9WHS1.1	O06393.1	P9WP69.1	P9WPN5.1	P9WNX3.1	O53380.1	I6YAU3.1
P0A4V2.1	P9WQP3.1	P0C2T2.1	P9WQP1.1	P9WQN9.1	O53311.1	P9WIS7.1	O06159.1
H2GU79.1	Q2G2Q0.1	P9WNV1.1	P9WNV5.1	Q8YE98.1	Q59191.1	P9WGY7.1	P9WGY9.1
Q2G2W1.1	P9WGH1.1	P9WNG9.1	P9WNG7.1	O84591.1	Q9Z7A6.1	P9WGR1.1	P96404.1
I6YGS0.1	Q6MX18.1	P9WNK5.1	O53692.1	P9WNK3.1	P9WNK1.1	P9WNJ9.1	P9WNJ7.1
P9WNJ5.1	P9WNJ3.1	P9WNJ1.1	P9WNI9.1	P96903.1	P9WNB1.1	P9WJE1.1	P9WJD9.1
P9WJD7.1	P9WJD3.1	P9WJC5.1	P9WJC3.1	P9WJC1.1	P9WNQ3.1	P9WJE5.1	P9WJC7.1
O84646.1	I6YDV4.1	P11439.1	Q5NFJ1.1	P9WNE5.1	P14738.1	P11089.1	H7C7G3.1
L7N6B9.1	I6XFI7.1	O05578.1	P96218.1	P9WN39.1	P9WN59.1	Q8YBI3.1	P9WN83.1
P9WJA9.1	P9WMY9.1	Q5NH51.1	O53673.1	P9WIP9.1	P0CE15.1	P72041.1	Q5NEM8.1
Q5NI16.1	P9WJA3.1	P0A4Q1.1	P9WIP1.1	P9WIN9.1	P9WNF5.1	O50846.1	Q59947.1
H7C7N8.1	Q5NEC6.1	O84606.1	P9WQJ9.1	P9WQJ7.1	P9WQ71.1	O53611.1	P9WKL1.1
P9WKJ7.1	D5V9Y8.1	P0CC04.1	P23700.1	P9WJN5.1	Q5NHJ0.1	Q5NEY9.1	P15917.1
Q2G155.1	O34094.1	Q8F8E1.1	O69661.1	H6MMU4.1	P9WK61.1	P9WK55.1	Q8YGS9.1
O50811.1	P9WQ59.1	P9WIN7.1	P9WIR1.1	O50430.1	D5VCH6.1	Q5NHI7.1	P9WFU9.1
I6XFY8.1	B2RH54.1	Q46409.1	P30690.1	A0A0J5IWN3.1	A0PSI5.1	A4TAC4.1	B1MB69.1
B2HSY2.1	B8ZSN3.1	E4WHS0.1	P9WK17.1	V5XE39.1	I6X7G8.1	I6Y461.1	I6YGB1.1
I6YC99.1	Q79FY7.1	I6X5Z8.1	I6Y479.1	I6YA32.1	O05461.1	Q2G1E2.1	P9WK19.1
I6YAW3.1	Q5NGG4.1	O51624.1	P9WJW5.1	Q50584.1	B2RHG1.1	Q5NFL7.1	P9WQN7.1
P9WHH3.1	O84639.1	Q5NF24.1	P9WJH1.1	P9WJH5.1	O53203.1	P55969.1	O50418.1
Q5NGE0.1	H7C7K8.1	O54584.1	G1UB30.1	Q5NH85.1	G1UB25.1	P0A3N8.1	E1X6Y5.1
Q5NEP7.1	Q8YHH0.1	P38006.1	P43838.1	P43839.1	P0CL67.1	P0CL66.1	Q0SLZ0.1
Q07337.1	G5IXI6.1	O07721.1	O53254.1	P75330.1	I6Y936.1	L7N649.1	L7N656.1
L7N693.1	Q79FK4.1	Q79FR3.1	Q79FR5.1	Q79G04.1	Q79FS8.1	Q6MWX1.1	Q79FV6.1
Q79FS5.1	Q79FQ7.1	Q79FP3.1	Q79FP2.1	Q79FK9.1	Q79FE6.1	I6XEF1.1	Q79FD4.1
Q6MX26.1	Q6MX50.1	L7N680.1	O53695.1	I6X8R2.1	O53246.1	I6Y0L1.1	Q2G282.1
P14283.1	P04977.1	P9WMX7.1	P9WFR1.1	P9WN09.1	O86345.1	P9WGU1.1	P9WGT9.1
P9WGT7.1	P9WPF7.1	P9WIB3.1	P9WMM9.1	P9WHM5.1	P9WQE9.1	Q8DQ08.1	Q8DQ07.1
I6Y231.1	P9WHV9.1	O05877.1	O07236.1	O86370.1	O06404.1	O06410.1	B8ZRL2.1
O06807.1	O33269.1	Q79FA9.1	Q79FK6.1	Q8VKN2.1	L7N675.1	Q79FK5.1	L0T7Y7.1
Q79FI9.1	Q79FE1.1	Q6MWX9.1	O84616.1	O84647.1	P9WQ27.1	O84288.1	I6X9S5.1
P9WJW3.1	P9WPS9.1	P95149.1	O53632.1	I6Y293.1	L0T243.1	P9WP43.1	P9WKC9.1
P96402.1	P71810.1	O06417.1	P96365.1	L0T5B2.1	P96264.1	P9WJK5.1	P9WJQ9.1
O84419.1	O84818.1	Q8YG32.1	O06608.1	O07175.1	P9WGA3.1	O53323.1	P96354.1
P9WIM9.1	B8ZRT2.1	P9WK93.1	P13423.1	O84583.1	P9WG63.1	P9WIM1.1	P9WKJ3.1
P9WNZ7.1	P9WK31.1	Q50701.1	P9WID3.1	Q8YC41.1	P9WPL3.1	P9WNI3.1	P9WNI7.1
P9WNI5.1	P9WQ49.1	P9WMG1.1	Q2GGR3.1	P9WK71.1	O33192.1	P9WND5.1	P9WFL9.1
P9WMB7.1	P9WJ79.1	P9WND7.1	Q63RA7.1	Q63ID0.1	I6YET7.1	Q9S010.1	P9WGC9.1
Q50700.1	Q5NFR6.1	P9WGK3.1	P9WHI1.1	P9WHV3.1	Q5NIA7.1	P9WG27.1	P9WF73.1
P9WGA1.1	P9WIB9.1	P9WGL3.1	O51381.1	P9WI83.1	P9WI79.1	P9WFT7.1	Q8YGS6.1
P05788.1	P17835.1	P9WIK9.1	Q5NHP7.1	P9WJU5.1	P9WGE7.1	Q2G2B2.1	P04958.1
P9WG67.1	P9WKE1.1	O07226.1	P9WJ13.1	P9WHF3.1	P9WF43.1	Q7D7L0.1	P9WMF9.1
P9WGN1.1	P9WKJ9.1	P60230.1	P9WKH7.1	O53699.1	P9WHT7.1	P9WJS5.1	Q5NII0.1
Q8YDZ3.1	Q9RPX7.1	P9WN67.1	O05576.1	Q5NHL4.1	P9WN15.1	P9WMD5.1	P9WMF5.1
P9WG85.1	P9WJW7.1	P9WIH1.1	P9WIG1.1	P9WIG3.1	P9WIF5.1	P9WIF1.1	P9WIE7.1
P9WHW9.1	P9WI41.1	P9WI39.1	P9WI37.1	P9WI25.1	Q11031.1	P9WI47.1	P9WI23.1
P9WI19.1	P9WI11.1	P9WI45.1	P9WI07.1	P9WI05.1	Q79FH3.1	P9WI43.1	P9WHZ7.1
P9WHZ5.1	P9WHZ3.1	P9WHY9.1	P9WHY7.1	P9WHY5.1	Q6MX07.1	P9WHY3.1	Q6MWY2.1
Q50703.1	P9WHX3.1	P96221.1	Q7D589.1	P9WMA3.1	P9WKW1.1	P9WKS9.1	P9WM29.1
P9WGC1.1	P9WLZ5.1	P9WLZ3.1	P9WLX1.1	P9WLV9.1	P9WLS7.1	P9WLQ1.1	P9WLJ1.1
P9WLH9.1	P9WLF3.1	P9WL97.1	P9WL87.1	P9WL85.1	P9WL83.1	P9WL67.1	P9WL63.1
P9WL51.1	P9WL47.1	P9WNH3.1	P9WGL7.1	P9WQM5.1	P9WPD9.1	A0A098A1N7.1	A0A098A2B0.1
A2RGM0.1	A5LVF6.1	A5MKZ9.1	B8ZQI8.1	B8ZQM3.1	B8ZQT5.1	B8ZR82.1	B8ZRH1.1
B8ZS71.1	B8ZS85.1	B8ZS86.1	B8ZSJ5.1	B8ZSL3.1	B8ZSL7.1	B8ZSM6.1	B8ZT30.1
B8ZTD0.1	B8ZTS2.1	B8ZTV5.1	B8ZU53.1	B8ZUA4.1	B8ZUE5.1	B8ZUF0.1	B8ZUT6.1
B8ZUX6.1	C0R9U8.1	C6DPT8.1	C6DQ35.1	E1XJN6.1	G8W6L3.1	G8W6L7.1	G8W6U7.1
H6MNY3.1	H6MQD5.1	H8HRN0.1	H8HW90.1	H8L8K3.1	I6TQ53.1	I6TX52.1	P0C5B9.1
Q1BYS7.1	R4MDK6.1	S5F815.1	W6GWM1.1	P9WFC9.1	P9WFJ9.1	P14916.1	P69996.1
P9WFC5.1	Q8VKQ6.1	P9WHS3.1	A5MKI6.1				

TABLE 5

LIST OF ACCESSION NUMBERS FOR FUNGAL ANTIGENS FROM IEDB and UNIPROT

Q5ANA3.1	Q5A3P6.1	Q59VM7.1	Q5A1A9.1	Q5APF0.1	Q8J0P4.1	Q4WHG0.1	Q4WQ87.1
Q59X67.1	Q59Z17.1	Q59ZI3.1	Q5AA33.1	B8N4Q9.1	Q4WAW6.1	Q4WAJ6.1	Q4X1V0.1
A0A1D8PQ86.1	Q59ZB1.1	Q873N2.1	Q59L72.1	B8NIF0.1	P46075.1	Q4WCL1.1	Q4WRP2.1
Q59L12.1	Q59LC9.1	P48989.1	Q5AFC2.1	B8N406.1	Q4WGL5.1	Q9HEQ8.1	Q4WVI6.1
P46593.1	P82611.1	Q5ADV5.1	Q59SG9.1	P41750.1	O00092.1	Q4WEN1.1	Q4WCV3.1
P0DJ06.1	O94038.1	Q59WD3.1	Q59RQ0.1	B8NM71.1	Q4WLW8.1	Q4WI37.1	Q4WNI1.1
P29717.1	P46589.1	Q59W04.1	Q59RK9.1	B8MYS6.1	Q8X176.1	Q4WZS1.1	Q4WQH4.1
Q9UW14.1	Q5AF56.1	Q59VN0.1	P31353.1	B8N8Q9.1	Q96UX3.1	Q4WDA4.1	Q4WDE1.1
Q92207.1	P83773.1	Q59WB9.1	Q5ACM4.1	B8N8R3.1	Q4WPF5.1	Q4WLS7.1	Q4WJT7.1
Q5A8T7.1	Q59YU1.1	Q59P53.1	Q5ACI8.1	B8N417.1	Q92450.1	Q4WWM6.1	Q4WLG1.1
Q5A8T4.1	Q59YV2.1	Q5A432.1	Q5AB93.1	B8N8R0.1	Q4WAW9.1	Q4WP81.1	Q4WQR6.1
P43076.1	Q5ABE5.1	Q5AK64.1	Q5ALL8.1	B8NM74.1	A4GYZ0.1	Q6MYT0.1	Q4WZS2.1
Q5AP53.1	Q59LF2.1	A0A1D8PNZ7.1	Q5A4X8.1	B8N106.1	Q4WAW3.1	Q4WTL0.1	Q4WXP0.1
Q5AL52.1	Q8NJN3.1	Q59Q30.1	Q5AD34.1	B8NHY4.1	Q70J59.1	Q4WXV2.1	Q4WU59.1
P43079.1	Q5ALN1.1	A0A1D8PN12.1	Q59V02.1	B8NJG8.1	Q4X1A4.1	Q4X0Z3.1	Q4WUG4.1
Q5AD07.1	Q59S72.1	Q5AK24.1	Q5AHC0.1	B8NM66.1	E9R876.1	Q4WN25.1	Q4WIK9.1
Q5A0E5.1	Q59K86.1	Q5AFT2.1	Q59Y11.1	B8MYL0.1	M4VQY9.1	Q4WN21.1	Q4WYP0.1
Q5AKU6.1	Q5AGD1.1	Q5A0W6.1	Q59QA5.1	B8NM62.1	Q4WF53.1	Q4X1N0.1	Q4X0B5.1
Q59RL7.1	P79023.1	P0CB63.1	Q5AMJ5.1	B8NGT5.1	Q4WZ64.1	Q4WQV2.1	Q4WYK9.1
G1UB61.1	Q59LP6.1	Q59U11.1	Q5AMF7.1	B8NM64.1	Q4WAZ0.1	Q4WZP2.1	Q4WY33.1
Q5ABC6.1	Q5AP87.1	P83775.1	Q5ABW2.1	B8NV37.1	Q4WR16.1	Q4WVK2.1	Q4X1F8.1
A0A1D8PQB9.1	P22274.1	Q5APF2.1	Q5APJ9.1	B8N151.1	Q4WLB9.1	Q4WUA0.1	Q4WA45.1
P87020.1	Q5AC48.1	Q59VP2.1	Q5AM72.1	B8NEJ3.1	Q4WQS0.1	A4DA84.1	Q4WKD7.1
P0CY27.1	Q5AP59.1	Q5AEE1.1	Q5ACU3.1	B8N8M2.1	Q4WEP7.1	Q4WJX0.1	Q4WCH5.1
Q59XX2.1	Q59MV1.1	Q5AMR5.1	Q5A1V3.1	B8MYV0.1	E9R9Y3.1	Q4WP38.1	Q4WXY3.1
Q59U10.1	Q5AL27.1	Q59SU5.1	Q59RF7.1	B8N7I7.1	P41748.1	Q4X1D7.1	Q4WPL7.1
Q59RW5.1	Q5AJD2.1	Q59VP1.1	Q5ACN3.1	B8NJG3.1	Q4WYG3.1	Q4W9Z9.1	Q4X136.1
Q59MQ0.1	P0CU38.1	Q5ADQ0.1	Q5AHE8.1	B8N8R1.1	P87184.1	Q4WE62.1	Q4WZ44.1
Q5ABU7.1	Q59QC5.1	Q5AK59.1	Q5AHA4.1	B8NJH2.1	Q4WBS1.1	Q4WZL3.1	Q4WTC7.1
Q9Y7F0.1	Q5A5N6.1	Q59RH5.1	Q5AEG7.1	B8NQ51.1	Q70DX9.1	Q4WB37.1	Q4WMK2.1
Q5AC08.1	Q59Q79.1	Q5ACW8.1	Q59V01.1	B8NM63.1	Q4WG16.1	Q4W9Z4.1	Q4WNC9.1
P30575.1	Q5AH38.1	Q5AGM0.1	Q5AK97.1	B8NM73.1	Q96X30.1	Q4WDD0.1	Q4WY67.1
Q5AAG6.1	Q5AMN3.1	Q59VN2.1	Q5A1B2.1	B8NYX0.1	Q4WV19.1	Q4WKB9.1	Q4WU12.1
O74189.1	Q5A1Z5.1	O94069.1	Q5AJK6.1	B8N3P7.1	Q4WAZ6.1	Q4WU07.1	Q4WA61.1
Q59W62.1	Q5A6K2.1	P0CY20.1	Q59L96.1	B8NJH1.1	Q4W944.1	Q4WBL6.1	Q4WA58.1
P0CY34.1	Q59L25.1	Q59XQ1.1	Q59MD0.1	B8MXJ7.1	Q4WTV7.1	Q4WX13.1	Q4WA60.1
Q5A1D3.1	Q5A922.1	O94048.1	Q5AG46.1	B8NJB0.1	Q4WMJ9.1	Q4WV71.1	Q4WX36.1
Q5AJU7.1	Q5AFG1.1	Q5ADX2.1	Q59VW6.1	B8NPS7.1	Q4WZ65.1	Q4X0C2.1	Q4WA62.1
Q5A4H5.1	Q5ALR8.1	P46586.1	Q5A8I6.1	B8N7Z8.1	A0A067Z9B6.1	Q4WRU4.1	Q4WA59.1
Q59Y31.1	Q5AEI2.1	P83776.1	Q9UW24.1	B8NSV5.1	Q66WM4.1	Q4WGS4.1	Q4WXQ7.1
P0CY29.1	Q5AI71.1	Q5A895.1	Q59Q38.1	B8MZA3.1	Q6T267.1	Q4WP13.1	Q4WVA0.1
Q5ANJ4.1	Q5ABA6.1	Q59PP0.1	Q5ADL0.1	B8NLY9.1	Q4WLW5.1	Q4WHG5.1	Q4WDN4.1
Q59NH8.1	Q5ABX0.1	Q5AHH4.1	Q5AH11.1	B8NR69.1	Q4WMJ0.1	Q4WPF7.1	Q4WK03.1
P0CY33.1	Q5A4N0.1	Q96UX5.1	Q59W55.1	B8MZ41.1	Q4WQU0.1	Q4WH83.1	Q4WCG2.1
Q00310.1	Q59TN9.1	P87206.1	Q5AC37.1	B8N7S7.1	Q4WMJ8.1	Q4WXW1.1	Q4WX99.1
Q5A0W9.1	Q5A5S7.1	Q5A029.1	Q5A7Q3.1	B8NR71.1	Q4WWN8.1	Q8NJM2.1	Q4WV10.1
Q5A4M8.1	Q59UG3.1	Q5A1E0.1	Q59PV6.1	A0A0D9MRV9.1	Q4WZ63.1	Q4WWD3.1	Q4WIS6.1
Q5AJC0.1	P0C075.1	Q59XL0.1	P0CH96.1	P55790.1	Q4WVN4.1	Q4WPU8.1	Q4WP65.1
Q59SU1.1	Q59R09.1	Q5A6U1.1	P83782.1	B8NM72.1	Q4WAY8.1	Q4WN99.1	Q4WUK1.1
Q5AG71.1	Q9B8D4.1	Q5A8I8.1	Q5A660.1	B8MW78.1	Q4WY07.1	P0C959.1	Q4WKN3.1
Q5AMT2.1	Q9B8D3.1	Q59PR9.1	Q59YT1.1	Q9P900.1	Q4WZ66.1	Q4X0S7.1	Q4WG58.1
Q59KY8.1	Q9B8D5.1	O74261.1	P53709.1	B8NDE2.1	Q4WQZ5.1	Q4WPW2.1	Q4WXX9.1
Q59LY1.1	Q59LR2.1	Q96VB9.1	Q5ACX1.1	B8NJF4.1	O42630.1	Q4X1U0.1	Q4WC37.1
Q59UT4.1	Q5AED9.1	Q5AQ47.1	Q5ADP9.1	B8NIV9.1	P0C7S9.1	Q4WP57.1	Q4X1Y0.1
Q5ABC5.1	Q5A4W8.1	Q5A985.1	Q92210.1	B8NG16.1	Q4WI46.1	Q4WPH9.1	Q4WZL8.1
Q59MV9.1	Q5ANH2.1	Q59ZW2.1	Q59MA3.1	B8NX60.1	Q4WQY4.1	Q4WDK5.1	Q4WR80.1
Q59MD2.1	Q5A649.1	P83784.1	Q5AFK3.1	B8NM75.1	Q4WAY3.1	Q4WI71.1	Q4WY53.1
Q5A8N2.1	Q5AI22.1	Q59P11.1	Q59S63.1	B8MZZ6.1	Q4WT66.1	Q4WYS7.1	Q4WL88.1
P40953.1	Q5A950.1	Q5ADN8.1	Q5A0Y2.1	B8NM67.1	Q6MY57.1	Q4WY08.1	Q4WGV9.1
Q5APR8.1	Q5ANC9.1	Q5A849.1	Q5ALW7.1	B8NRX2.1	P0C954.1	Q4WND3.1	Q4WC29.1
P10613.1	Q59UH7.1	Q5A7R7.1	Q59W52.1	B8NXJ2.1	Q4W946.1	Q4X1D2.1	Q4WKV8.1
Q5A5Q6.1	Q5ALX8.1	Q59XB0.1	Q59S42.1	B8NMD3.1	Q4WMJ5.1	Q6MY91.1	Q4WYA5.1
Q5A4F3.1	Q5AI37.1	Q59P96.1	Q5A961.1	B8NBI2.1	Q70GH4.1	Q4WRV2.1	Q4WCM6.1
P43094.1	Q5ABV4.1	Q59SR6.1	Q59ST6.1	B8NPA4.1	Q4WUL6.1	Q4WRX4.1	Q4WKB2.1
Q9P940.1	Q5AKU4.1	Q9P975.1	Q59N74.1	B8N803.1	P61832.1	Q4WP03.1	Q4WNG7.1
Q5AJY5.1	Q59VY1.1	O94083.1	Q5A6P6.1	B8NPT0.1	Q4WG11.1	Q4WTA6.1	Q4WRE8.1
P39827.1	Q59Z51.1	Q5AIA4.1	Q59XM0.1	B8MXP5.1	Q4WYU4.1	Q4WZJ0.1	Q9P8P4.1
Q59WF4.1	Q59LV8.1	Q59YF4.1	Q5A4N5.1	B8NIB8.1	Q4WYR6.1	Q4W9S8.1	Q4WJS4.1
P83774.1	Q59X11.1	Q59XW9.1	Q5A6M2.1	B8N9H4.1	Q4WNE1.1	Q4X054.1	Q4WHW1.1
Q59Q46.1	Q5ABQ7.1	Q59WU8.1	Q5A5M7.1	B8NNK9.1	Q4WQZ6.1	Q4X1I3.1	Q4WYG7.1
Q59X23.1	Q59PZ3.1	Q5AAR0.1	Q5A6N8.1	B8NI03.1	Q4WWC6.1	Q4W9V1.1	Q4WJH4.1
P46614.1	O13332.1	Q5AQ62.1	Q9UVJ4.1	B8NM76.1	Q6Q487.1	Q4WDF1.1	Q4WJM6.1
Q5AQ33.1	Q5AHD6.1	Q59R35.1	Q59V88.1	B8NM79.1	P0C957.1	Q4WWN2.1	Q4WMB6.1
P82610.1	A0A1D8PPG4.1	Q5A847.1	Q59RA0.1	B8NJG9.1	Q4WM08.1	Q4WTH0.1	Q4WMU9.1
Q5AP80.1	Q5ADW3.1	Q5A6A4.1	Q59XU5.1	B8NPL7.1	Q4W9B8.1	Q4WJQ1.1	Q4WIF3.1

TABLE 5-continued

LIST OF ACCESSION NUMBERS FOR FUNGAL ANTIGENS FROM IEDB and UNIPROT

P46598.1	Q5AML6.1	Q5A4Q1.1	Q5AH12.1	B8NMR5.1	Q4WWJ1.1	Q4WKL7.1	Q4WEH7.1
Q5A506.1	Q5A846.1	P0CY22.1	Q59ZX3.1	B8NP65.1	E9RCR4.1	Q4WX90.1	Q4WT34.1
Q5A599.1	A0A1D8PPI5.1	P42800.1	Q5AB48.1	B8N5S6.1	Q4WM67.1	Q4WG69.1	Q4WT99.1
Q59NP5.1	P0CT51.1	Q59KI4.1	Q5A3Q0.1	B8NJ86.1	Q4WUN7.1	Q4WM32.1	Q4X0N1.1
Q5AHA0.1	Q59MA6.1	Q59JU3.1	Q5A6M0.1	P41747.1	E9QRF2.1	Q4WTI3.1	Q4WSA8.1
Q07730.1	Q5ALW2.1	P83777.1	Q5AL29.1	P41765.1	Q4WK60.1	Q4WHX4.1	Q4WLD1.1
Q5AD05.1	Q5ABU8.1	Q5A310.1	Q59KG2.1	B8N6V7.1	Q4WZ61.1	Q4WXE9.1	Q4WMU5.1
Q5AME2.1	Q5AEC6.1	Q59N80.1	O42825.1	B8NKE9.1	Q4W945.1	Q4X0X6.1	O13410.1
P41797.1	Q5A4X0.1	Q5AJ77.1	O59931.1	B8NGU6.1	Q4WMA6.1	Q4W8Z9.1	Q4WG40.1
P0CY24.1	Q59LX9.1	Q59ZV4.1	Q5AM44.1	B8NBP9.1	Q4WNS8.1	Q4WEB4.1	Q4WLD5.1
Q5ACZ2.1	Q59PE7.1	Q59XA7.1	Q59RP7.1	B8N8R2.1	Q4WDE9.1	Q4WDH3.1	Q4WLD4.1
Q5ABE2.1	Q5ACL9.1	Q59L13.1	Q5AK94.1	B8NKI4.1	Q4WUR1.1	Q4X1N4.1	Q4WLD2.1
Q59M56.1	Q5ABT8.1	Q5AG97.1	Q5AKB1.1	B8NQQ7.1	Q4WQ08.1	Q4WMP0.1	Q4WLC9.1
Q5AK51.1	Q5AMH3.1	Q5AB15.1	Q59VM4.1	B8NJH0.1	Q4WF61.1	A4D9B6.1	Q4WQ54.1
Q59UT5.1	Q5AEF0.1	Q59S66.1	Q5A246.1	B8NKB9.1	Q7LKT3.1	Q4WD45.1	Q4WAZ8.1
Q5AAF4.1	Q5AJC1.1	Q59KN8.1	Q5AJ92.1	B8NM78.1	Q4WQZ3.1	Q4WM95.1	Q4X161.1
G1UBC2.1	Q59VP0.1	Q5A8X9.1	Q5A2V2.1	B8NTP7.1	Q4WAZ3.1	Q4X0I8.1	Q4WB00.1
Q5ADT1.1	Q5AGC7.1	Q5AFP8.1	Q5ABP8.1	B8MWJ5.1	Q4WNV0.1	Q4WLV6.1	Q4WQ14.1
O59923.1	Q5AQ12.1	Q9P8W1.1	Q5AAV3.1	B8N7G5.1	Q4WRZ5.1	Q4W9R2.1	Q4WP12.1
Q5AL03.1	Q59X94.1	Q9P8W0.1	Q59SN0.1	B8NER4.1	Q4WPF2.1	Q4WAW8.1	Q4WCR3.1
Q5A2Z7.1	Q5AFX2.1	Q9P4E7.1	Q5ACU6.1	B8NJH3.1	Q8TFZ1.1	Q4WMS0.1	Q4WAQ9.1
Q59VH7.1	Q5A1E3.1	Q9P8V9.1	Q9Y7C4.1	B8NDL1.1	Q4WB03.1	Q4WAW5.1	Q6MYX6.1
Q59KZ1.1	O43101.1	Q5A7Q6.1	Q9HFQ7.1	B8NWY6.1	P40292.1	Q4WAX0.1	Q4WZJ6.1
Q5A960.1	Q59WU0.1	Q5A6N1.1	Q5A3J1.1	B8NC58.1	Q4WPN0.1	Q4WTQ4.1	Q4WP59.1
Q5AFA2.1	Q5A893.1	Q5AI58.1	P40910.1	B8NIM4.1	Q4X1D4.1	Q4WJ80.1	Q4WLC8.1
Q5A5U4.1	P43069.1	Q9P4E5.1	Q5AQ57.1	B8NXI4.1	Q4WBW4.1	Q4WD43.1	Q4WVM1.1
Q5AQ36.1	Q59LN9.1	P0CH67.1	Q5ACL4.1	B8NJG5.1	Q4X180.1	Q4WD44.1	Q4WLP9.1
Q9URB4.1	Q5AA40.1	Q5A387.1	Q5A449.1	B8NYD8.1	Q4WQZ4.1	Q4WD46.1	Q4WHD2.1
Q5AL36.1	Q59S45.1	Q59NB8.1	Q59S27.1	B8NYX1.1	Q4WZ69.1	Q4WD48.1	Q4W9T6.1
P86029.1	Q5AM60.1	Q92209.1	Q59VF9.1	B8NX76.1	Q4WFK4.1	Q4WD42.1	Q4WR79.1
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
Q5A651.1	Q5AG86.1	Q59PT4.1	Q5AJ85.1	B8N2I5.1	Q4WWC5.1	Q4WMJ1.1	Q4WYA1.1
Q59YH3.1	Q59ST8.1	Q5AKW3.1	Q59P44.1	B8NP78.1	Q4WTN9.1	Q4WBL2.1	Q6MY48.1
P82612.1	O93803.1	Q9P4E8.1	Q59KC4.1	B8NE46.1	Q4WR17.1	Q4WIQ0.1	Q9UUZ6.1
P53705.1	Q5AFT3.1	Q9P4E6.1	Q59XV0.1	B8NMK3.1	Q4WA15.1	Q4WID9.1	Q4WRH5.1
Q5AMQ6.1	Q5A519.1	Q59MJ2.1	Q5ABV6.1	B8NG97.1	Q4WZ11.1	Q4WPG0.1	Q4WEU2.1
Q9Y7W4.1	O74161.1	Q59LL4.1	Q59UH5.1	B8N316.1	E9RD40.1	Q4WDM5.1	Q8NKF4.1
Q5A688.1	Q59RN6.1	Q59S43.1	Q5A869.1	B8NYW9.1	A4DA85.1	Q4WYV0.1	Q9HGV0.1
P25997.1	Q5A3Z5.1	Q59P87.1	Q5AEF2.1	B8NBJ4.1	P54267.1	Q4WEY4.1	Q4X156.1
Q5AHG6.1	P31225.1	Q5AEN6.1	Q5A0W7.1	B8N7E5.1	P0C958.1	Q4WN24.1	Q4WXZ5.1
Q8TGH6.1	Q59QC6.1	Q59LF9.1	P83783.1	B8NM69.1	Q4WQZ7.1	Q4WQ21.1	Q4X1R1.1
Q5ABD0.1	Q9I589.1	Q5ADX5.1	Q59XP0.1	B8N306.1	Q9Y8D9.1	Q4WNN2.1	Q4WXX4.1
Q5AL16.1	Q5A8W9.1	P83778.1	Q5AP66.1	B8N7Z0.1	Q4WBR2.1	Q4WAH2.1	Q4WJE9.1
Q59RR0.1	Q5APG6.1	Q5AG31.1	Q5AGZ9.1	B8NJB2.1	Q4WL66.1	Q4WT40.1	P41746.1
Q59KM8.1	Q59YD9.1	Q5AHZ7.1	Q5AFE4.1	B8NWE1.1	Q4WVG8.1	Q4WFT3.1	Q4WDF7.1
Q5A220.1	Q5AEN1.1	Q5ACU4.1	Q59PE4.1	B8NIM7.1	Q4WZ68.1	Q4WQM4.1	Q4X0T4.1
Q92206.1	Q8X1E6.1	Q59PD6.1	Q59LF3.1	B8NKA3.1	Q8TGG8.1	Q4X0W8.1	Q4WNX1.1
Q59Z29.1	P56553.1	Q5A940.1	Q9P8E3.1	B8NK45.1	Q4X0A9.1	Q873N1.1	Q4WTM9.1
Q5AK66.1	Q59WI7.1	Q59M70.1	Q59S78.1	B8NBX4.1	Q4WHG1.1	Q4WR23.1	Q4WQM6.1
P46273.1	Q5ALY0.1	Q5A917.1	Q59L89.1	B8NVK8.1	Q4WVE3.1	Q4WEI5.1	Q4WV66.1
Q5AFI4.1	Q5A0A9.1	Q5ANA8.1	P46250.1	B8NI10.1	Q4X162.1	Q4WE68.1	Q4WKH9.1
Q5ALV2.1	Q5A884.1	Q5A3M6.1	Q5AQ76.1	B8NSW2.1	Q6A3P9.1	Q4WR21.1	Q4WI01.1
Q5A312.1	Q9B8D8.1	Q59MC8.1	Q5AI21.1	B8NA06.1	Q4WQI1.1	Q4WTC4.1	Q873W8.1
Q5A3V6.1	Q59PZ7.1	Q5A3K2.1	Q96W54.1	B8NLL0.1	O43102.1	Q4WPV8.1	Q4WPW8.1
Q59TB2.1	Q9B1P9.1	Q5A644.1	P0CU35.1	B8NBB2.1	Q7Z8P9.1	Q4WYF1.1	Q4X1W8.1
Q59KI0.1	Q59MA9.1	Q59ZH9.1	O94150.1	B8NBM3.1	Q4WAY4.1	Q4WJM7.1	Q4WV30.1
Q5APU2.1	Q5ACH7.1	Q71U11.1	Q5ADT9.1	B8NA66.1	Q4X1Q4.1	Q4WHP5.1	Q4WUG9.1
O42766.1	P0C8K9.1	Q5AJF1.1	Q5A0L9.1	B8NUL8.1	Q4WJ90.1	Q4WHU1.1	Q4WYF4.1
Q5A446.1	Q59MF9.1	Q59YV0.1	Q5ACV9.1	B8N076.1	Q4X117.1	Q4WT68.1	Q4WK80.1
Q59UY7.1	Q5AI44.1	Q59S85.1	Q5A1D5.1	B8NVB7.1	Q4WBU0.1	Q4U3Y2.1	Q4WGU1.1
Q5A6T5.1	Q5AL10.1	Q59PP6.1	Q5A744.1	B8NBC2.1	Q4X228.1	Q4WSM6.1	Q4WYK1.1
G1UB63.1	Q5AED6.1	Q59X40.1	Q5A455.1	B8NJL4.1	Q6MYX3.1	Q4W9B9.1	Q4WNC1.1
Q59QC7.1	Q5AGE5.1	O94030.1	Q5AAU3.1	B8NR70.1	Q4X084.1	Q4WHB7.1	Q4WQC5.1
P34948.1	Q59LQ5.1	Q5AL63.1	Q9C0L9.1	B8NGP8.1	Q4X251.1	Q4WNA1.1	Q4WJS7.1
P46592.1	P0C8L0.1	Q5A0Y8.1	Q5AFV3.1	B8NXS9.1	Q4WHZ9.1	Q4WHH4.1	Q4WHK3.1
Q5A872.1	Q5A301.1	Q5A723.1	Q5A360.1	B8NDZ1.1	Q4WLA7.1	Q4WA21.1	Q4X0M4.1
Q59QW5.1	Q59X26.1	Q5A1A0.1	Q5AI90.1	B8NW70.1	Q4WXH8.1	Q4WCP8.1	Q4WLI5.1
Q59WH0.1	Q5AML2.1	Q5A4G2.1	Q5AD73.1	B8MW97.1	Q4WAS9.1	Q4WVH0.1	Q4WP54.1
Q5A1N6.1	Q59W50.1	Q5A970.1	Q5AD77.1	B8N9M2.1	Q4WZ60.1	Q4WUJ6.1	Q4WNH8.1
Q5AAJ8.1	Q59ZG8.1	Q59Y46.1	P87219.1	B8N195.1	Q4WYG2.1	Q4WWP1.1	Q4WTT2.1
Q5AG40.1	Q59VC6.1	Q5AHC2.1	Q59QH6.1	B8MYS5.1	A4D9R3.1	Q4WS57.1	Q4WEL6.1
Q59P39.1	Q59ZY9.1	Q59V93.1	Q59PT6.1	B8NNI2.1	Q4WR20.1	Q4WVD9.1	Q4WI38.1
Q5AJB1.1	Q5AL13.1	Q59SI5.1	Q5A5N5.1	B8NJZ7.1	Q4WA22.1	Q4WK77.1	Q4WTT7.1
Q59UP6.1	Q59NY7.1	Q59RR3.1	Q5ADL4.1	B8N6H2.1	Q4WM60.1	Q4WCL2.1	Q4WWS3.1

TABLE 5-continued

LIST OF ACCESSION NUMBERS FOR FUNGAL ANTIGENS FROM IEDB and UNIPROT

Q5AMH6.1	Q5AP89.1	Q5APQ8.1	Q5AM84.1	B8NIX4.1	Q0H904.1	Q4WN75.1	Q4WVH3.1
Q59SF7.1	Q59XY0.1	P87207.1	Q5AK73.1	B8NGC8.1	P78574.1	Q4WES5.1	Q4WD95.1
Q59VX8.1	Q5ADL9.1	Q59MZ9.1	Q5A4H9.1	B8N970.1	Q4WAR8.1	Q4WVT3.1	Q4WLP1.1
Q59WG7.1	P53698.1	Q59Y41.1	Q5ALX5.1	B8MY73.1	Q4WNK7.1	Q4WVV6.1	Q4WQI6.1
Q5AFN8.1	Q5AJX2.1	Q59S52.1	Q5A748.1	B8N6W5.1	P78746.1	Q4WP83.1	Q4WCJ7.1
Q59TP1.1	Q5APS5.1	Q59U73.1	Q5ALU2.1	B8N3L3.1	Q4WPF8.1	Q4WAY7.1	Q4WTT8.1
Q5AF39.1	Q59PG6.1	Q9Y872.1	Q5A2B9.1	B8NPS8.1	Q4WX43.1	Q4WX89.1	Q4WWR2.1
Q5AP97.1	Q59NP1.1	Q5AGA9.1	Q5ALX3.1	B8NTI4.1	Q4WQL4.1	Q4WYT0.1	Q4WWL0.1
Q5A5U9.1	Q59PD3.1	Q59VL7.1	Q5A1M3.1	B8MYS7.1	Q4WBE1.1	Q4WNT9.1	Q4WZT9.1
Q5AF41.1	Q5ACW2.1	Q59KJ7.1	Q5A4H4.1	B8NM70.1	Q4WQT2.1	Q4WVS4.1	Q4X0I7.1
O13318.1	Q5ANB2.1	Q5AP90.1	Q5AA26.1	B8MYS8.1	Q4WBT5.1	A4D9J5.1	Q4WU00.1
Q5AA09.1	Q5AJD0.1	Q5AD72.1	Q5ANL6.1	B8N6M6.1	Q4WQZ2.1	Q4W9B7.1	Q4WRW0.1
Q5A762.1	Q5A4P9.1	Q59S59.1	P87218.1	B8NCU7.1	Q4WD47.1	Q4WNC6.1	Q4W9V0.1
P46587.1	P78599.1	Q5APM7.1	Q59KF3.1	B8N5T6.1	Q4WCZ8.1	Q4WJW8.1	Q4WYJ7.1
Q5A287.1	Q5APC8.1	Q5A2Z1.1	Q59N29.1	B8MVS3.1	Q4WB01.1	Q4WH96.1	Q4WHY5.1
Q59X49.1	Q59LU0.1	Q59TD3.1	Q5A0L7.1	B8NCM8.1	Q4WBK6.1	Q4X0I5.1	Q4WEP0.1
Q5ADM9.1	Q5APT8.1	P84149.1	Q59UG4.1	B8NW36.1	Q4WRQ7.1	Q4WMS9.1	Q4WXD3.1
Q5AH02.1	Q59PR3.1	Q5AI97.1	Q5AHK2.1	B8NJG7.1	Q4WTQ6.1	Q4WAH4.1	Q4WJ02.1
Q5A4X5.1	Q5A2W2.1	Q5A2A2.1	Q5ADP6.1	B8N7Z6.1	Q4WJ21.1	Q4WII3.1	Q4WP96.1
Q5A4E3.1	Q5A4E2.1	Q5A044.1	Q5AK62.1	B8NGU1.1	Q4WPQ8.1	Q4WJA1.1	Q4WN54.1
Q5A761.1	Q5A309.1	Q59P03.1	Q59YF0.1	B8NC10.1	Q4WR62.1	Q4W9R7.1	Q4WCW2.1
Q9UW23.1	A0A1D8PL26.1	Q59TU0.1	Q5AAJ7.1	B8N4P0.1	Q4WD56.1	Q4WPP2.1	Q4WPM6.1
P53704.1	P0CU37.1	Q5APK7.1	Q5A8H7.1	B8NPN0.1	Q4WIN6.1	Q4WNQ6.1	Q4WNW3.1
Q59VR1.1	Q5AF95.1	Q59ST1.1	Q59U81.1	B8NQ08.1	Q4U3E8.1	Q4WNI0.1	Q4WSI0.1
G1UB67.1	Q59MW2.1	Q5A7N3.1	Q5APB6.1	B8N3N5.1	Q4X195.1	Q4WDG1.1	Q4WNY4.1
P52496.1	Q59S50.1	Q5ANP2.1	Q59WD5.1	Q00049.1	P0C955.1	Q4X0Z7.1	Q4WVF4.1
Q9HEW1.1	Q5AD78.1	O59933.1	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	B8MZI5.1	Q4WQY6.1	Q4WPE6.1	Q4WI88.1
Q5AJ71.1	Q59NX9.1	Q5A687.1	Q59R24.1	B8NSJ0.1	Q4WXK4.1	Q4WWW9.1	Q4WQL0.1
O74201.1	Q5A119.1	Q59R28.1	Q5AHJ5.1	B8NDR8.1	Q4WI96.1	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	B8NLN6.1	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	Q4WI16.1
Q5A477.1	Q5AGC4.1	Q59N20.1	P48990.1	B8NSD4.1	Q4WJJ3.1	Q4WMG1.1	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	B8N0Q7.1	Q4WMU3.1	Q4WGB7.1	Q4WIQ2.1
Q9UWF6.1	Q59QD6.1	Q59S06.1	Q59TN1.1	B8N513.1	Q4WQG5.1	A4DA73.1	Q4X022.1
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	B8NHF2.1	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	Q4WI37.1	Q4WXT2.1
Q5AP52.1	Q5A1U8.1	Q59VX9.1	Q59NW5.1	B8NPX1.1	Q92197.1	Q4WZS1.1	Q8J130.1
P0CY31.1	O74198.1	Q59YD8.1	Q5A6Q4.1	B8NYW8.1	Q4WSE8.1	Q4WDA4.1	Q4WJX5.1
P13649.1	Q5A013.1	Q59QH0.1	P43075.1	B8N219.1	Q4WX94.1	Q4WLS7.1	Q4X1I8.1
Q5AG77.1	P87163.1	Q5A8A2.1	Q59Q36.1	B8NQK0.1	Q4WLD0.1	Q4WWM6.1	Q4WVW4.1
Q9UW13.1	Q5AI86.1	Q9B8D7.1	Q92410.1	Q12732.1	Q4WUK5.1	Q4WP81.1	Q4WTH1.1
P0CU34.1	Q5AM80.1	Q9UW25.1	Q5A1M4.1	Q9HEY7.1	Q8TGG5.1	Q6MYT0.1	Q4WLI9.1
P40954.1	Q5A6Q7.1	Q59XY9.1	Q5ANC8.1	Q6UEG8.1	Q4WTK9.1	Q4WTL0.1	Q4WQJ5.1
Q04802.1	Q5AGV4.1	Q5A2T0.1	Q5A4K7.1	O42716.1	Q4WVU5.1	Q4WXV2.1	Q4WQJ2.1
P0CY35.1	Q5AJ82.1	Q5AGW8.1	Q5ADL8.1	Q9UW95.1	Q4WLM7.1	Q4X0Z3.1	Q4WK56.1
Q5AAU5.1	Q5AIA1.1	Q5ADS3.1	Q59RQ2.1	Q9Y8D9.1	Q4W9P4.1	Q4WN25.1	Q4WJS2.1
Q59VQ8.1	Q5A9Z6.1	Q5ACR4.1	Q5APC0.1	A2SZW8.1	Q4WIT0.1	Q4WN21.1	Q4WJT9.1
Q59VF4.1	Q5AGC1.1	P0CU36.1	Q5A931.1	Q2U2U3.1	Q4WQB9.1	Q4X1N0.1	Q4WUV8.1
Q5A0X8.1	Q59ZV5.1	Q5A2Y7.1	Q59VW7.1	Q00258.1	Q4WGK6.1	Q4WQV2.1	Q4WX68.1
O13426.1	Q59VP7.1	Q5A368.1	Q5AKU5.1	Q12437.1	Q4WMR0.1	Q4WZP2.1	Q4WHN8.1
Q5A0M4.1	Q5A7P3.1	Q9B8D6.1	Q59MN0.1	E9QYP0.1	Q4WYE5.1	Q4WVK2.1	Q4WJU8.1
Q59PF9.1	Q5A6K8.1	Q9B8D0.1	Q59WH7.1	Q4WS76.1	Q4WZ01.1	Q4WUA0.1	Q4WBT4.1
Q5AFP3.1	Q5AD13.1	Q5A2K0.1	Q96WL3.1	Q4WMJ7.1	Q4W930.1	A4DA84.1	Q4WZV6.1
Q5AEK8.1	Q04782.1	Q5A1Q5.1	Q59ZX6.1	P28296.1	Q4WBR0.1	Q4WJX0.1	Q4WUV9.1
Q5AFK0.1	Q5A0J9.1	Q5AEM5.1	Q59MU1.1	E9RAH5.1	Q4WHD1.1	Q4WP38.1	Q4WLV2.1

TABLE 5-continued

LIST OF ACCESSION NUMBERS FOR FUNGAL ANTIGENS FROM IEDB and UNIPROT

Q5APD4.1	Q59ZZ6.1	Q5AK25.1	Q5A0J0.1	Q4WW81.1	Q4WTB3.1	Q4X1D7.1	Q4WFS2.1
Q5ADQ9.1	Q5AH25.1	Q5AK10.1	Q59WK2.1	Q50EL0.1	Q4WRV9.1	Q4W9Z9.1	Q4WBM1.1
P83779.1	Q59XM1.1	Q5AI15.1	P43073.1	Q4WY82.1	Q4X267.1	Q4WE62.1	Q4WAU7.1
Q5AAH2.1	Q59NN8.1	Q5AEM8.1	P87220.1	Q4WSF6.1	Q4WVZ3.1	Q4WZL3.1	Q4WZS3.1
O74254.1	Q5AP65.1	Q5A4J4.1	Q5ABD9.1	E9RCK4.1	Q4WR24.1	Q4WB37.1	Q4WPU9.1
Q5AL49.1	Q5AFF7.1	Q59YK4.1	P83781.1	Q4WZA8.1	Q4WPM8.1	Q4W9Z4.1	Q4WVZ0.1
P53697.1	Q59VR3.1	Q59WV0.1	Q5ANB1.1	Q4WAW7.1	Q4WE86.1	Q4WDD0.1	Q4WCX9.1
Q5ACL7.1	Q5AFH3.1	Q5AHB1.1	Q5A0E2.1	Q92405.1	A4DA70.1	Q4WKB9.1	Q4WJ38.1
Q5AEM6.1	P83780.1	Q5APK0.1	Q5AMG5.1	Q4WRY5.1	Q4WW45.1	Q4WU07.1	Q4WRC2.1
Q8TG40.1	Q5A4G9.1	Q59PW0.1	Q5A6T8.1	Q7Z7W6.1	Q4WVG2.1	Q4WBL6.1	Q4WWW5.1
Q59X38.1	Q59NQ9.1	O74711.1	Q59WG5.1	Q4WZ67.1	Q4WQG9.1	Q4WX13.1	Q4WC84.1
Q59VQ3.1	A0A1D8PNP3.1	Q5ADN9.1	Q5AI80.1	Q4WZB3.1	Q4WQN1.1	Q4WV71.1	Q4WTW3.1
Q5A7Q2.1	Q5A9Z1.1	Q5ACP5.1	Q5AB49.1	Q4WLN1.1	Q4WCF1.1	Q4X0C2.1	Q4WFV6.1
Q5AJV5.1	A0A1D8PK89.1	Q5A1E1.1	Q59R32.1	Q4WR82.1	Q4WZC3.1	Q4WRU4.1	Q4WKD9.1
Q5A3Z6.1	Q59WB3.1	Q59L86.1	Q5A061.1	O14434.1	Q4WYX7.1	Q4WGS4.1	Q4WP10.1
Q5A201.1	Q59ZC8.1	Q5AD23.1	Q59P50.1	Q4WMK0.1	Q4X0A5.1	Q4WP13.1	C5JZM2.1
O93827.1	Q5A1L6.1	Q5A5U6.1	Q59WC6.1	Q4WPX2.1	Q4WUD3.1	Q4WHG5.1	P0DJ06.1
Q5AAI8.1	A0A1D8PN14.1	Q5ADQ7.1	Q5AI48.1	O43099.1	Q4WS49.1	Q4WPF7.1	P46598.1
Q5A2J7.1	Q5A8X7.1	Q59WJ4.1	Q59ZU1.1	Q4WJ81.1	Q4WCX7.1	Q4WH83.1	P87020.1
P22011.1	Q59X39.1	Q5AGV7.1	Q5AG56.1	P67875.1	Q4WXX5.1	Q4WXW1.1	P38110.1
Q9HGT6.1	Q5ACW6.1	Q59NR8.1	Q59T36.1	Q4WZB4.1	Q4WNB5.1	Q8NJM2.1	C1GK29.1
Q9UW26.1	P0CB54.1	Q5A5K7.1	Q9P840.1	E9QUT3.1	O42799.1	Q4WWD3.1	
Q59LX5.1	A0A1D8PN88.1	Q5A210.1	Q5AHB8.1	Q4WAZ9.1	Q4WHA3.1	Q4WPU8.1	
Q59PT0.1	A0A1D8PMB1.1	Q59N10.1	Q5AKU3.1	Q4WZ70.1	Q4W9M3.1	Q4WN99.1	
Q3MNT0.1	Q5ABR2.1	Q5A1B3.1	Q59ZW4.1	E9RBR0.1	Q4WVH5.1	P0C959.1	

TABLE 6

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

	P19594.1	P28335.1	P29000.1
P49148.1	Q6R4B4.1	P42037.1	Q9HDT3.1
P00304.1	Q2KN24.1	Q2KN27.1	P43174.1
Q7Z1K3.1	A1IKL2.1	Q7M1X6.1	P49372.1
O82580.1	Q647G9.1	Q9SQH1.1	C7E3T4.1
P40292.1	P28296.1	P79017.1	Q96X30.1
Q09097.1	P04403.1	P15494.1	P25816.1
P13916.1	Q9UAM5.1	P54958.1	D0VNY7.1
A0ERA8.1	Q8MUF6.1	A7IZE9.1	O96870.1
P00711.1	P02754.1	P02769.1	P02662.1
Q14790.1	E9R5X9.1	Q96385.1	Q7M1E7.1
P42040.1	P42059.1	P0C0Y5.1	P02465.1
Q9ATH2.1	Q8W1C2.1	P18632.1	P43212.1
O04701.1	O04725.1	P94092.1	P04800.1
O04298.1	Q58A71.1	Q23939.1	Q967Z0.1
Q00855.1	P49275.1	Q26456.1	P08176.1
Q9Y197.1	P14004.1	P49273.1	Q7Z163.1
Q95182.1	P41091.1	O15371.1	P25780.1
Q7XAV4.1	P04075.1	Q90YL0.1	P01005.1
P02227.1	Q9NJQ6.1	O65809.1	P26987.1
P12031.1	P15252.1	Q7Y1X1.1	P52407.1
P43216.1	O23972.1	P24337.1	Q7Y1C1.1
P81295.1	O64943.1	P07498.1	Q84UI1.1
Q7M1X5.1	P14947.1	P14948.1	Q5TIW3.1
P11589.1	P43211.1	P40967.1	Q01726.1
P12036.1	Q15233.1	Q5RZZ3.1	Q8GZB0.1
P22895.1	P43217.1	P55958.1	B8PYF3.1
K7VAC2.1	Q3Y8M6.1	Q9URR2.1	Q9P8G3.1
P00433.1	Q41260.1	P56164.1	Q40967.1
Q5ZQK5.1	Q40960.1	P43215.1	O82040.1
Q9FPR0.1	B6T2Z8.1	Q9C5M8.1	P15722.1
E3SH28.1	O65457.1	B6RQS1.1	P02761.1
Q8L5K9.1	C1KEU0.1	Q91482.1	Q9XHP1.1
O00267.1	D2T2K3.1	Q9T0P1.1	Q07283.1
O15205.1	O00762.1	D2KFG9.1	H9AXB3.1
Q2VST0.1	ABL09307.1	ABL09312.1	AGC39172.1
AGC39168.1	CAM31908.1	ABB77213.1	P83958.1
CAM31909.1	P85206.1	P86137.2	P85524.1
AGC39164.1	AGC39165.1	AGC39166.1	AGC39167.1
AAC37218.1	P50635.2	XP_001657556.2	P18153.2
XP_001654291.1	ABF18258.1	XP_001655948.1	XP_001655954.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

AAB24432.1	CAA76831.1	AAB47552.1	AAM77471.1
P49148.1	Q6R4B4.1	P78983.2	Q00002.2
OWY50380.1	AAO91800.1	P0C0Y4.2	AGS80276.1
P27759.1	P27760.1	P27761.1	P28744.1
CBW30989.1	CBW30990.1	CBW30991.1	CBW30992.1
P27762.1	CBJ24286.1	CBK52317.1	CBK62693.1
CBK62699.1	O04004.1	AAP15203.1	AAP15202.1
5EV0_B	AAX77684.1	AAX77685.1	AHA56102.1
AAA20067.1	AAA20064.1	AAA20066.1	AAA20068.1
AAN76862.1	AAL91665.1	O23791.1	Q94JN2.1
AGC60020.1	Q7Z1K3.1	AGC60035.1	AGC60036.1
BAJ78223.1	AGC60029.1	AGC60030.1	AGC60031.1
AEQ28167.1	P83885.1	CAK50389.1	BAF43534.1
BAF75706.1	BAF75707.1	BAF75708.1	BAF75709.1
CAB58171.1	G37396	Q7M1X6	Q7M1Y0
P00630.3	ABF21077.1	ABF21078.1	Q08169.1
NP_001119715.1	NP_001035360.1	ABD51779.1	NP_001011564.1
AHM25036.1	AHM25035.1	P49372.1	P92918.1
AAB22817.1	P43237.1	P43238.1	AAT00595.1
3S7E_A	B3EWP3.1	C0HJZ1.1	B3EWP4.1
AAC63045.1	AAD47382.1	AAM46958.1	AAM93157.1
AAD55587.1	ADB96066.1	AGA84056.1	AAD56337.1
ABW17159.1	AAQ91847.1	ABP97433.1	ACA79908.1
AAU21500.1	AAZ20276.1	Q45W86	CAG26895.1
AHF71024.1	AHF71025.1	AHF71026.1	AAO24900.1
ACE07188.1	ACE07189.1	CAD12861.1	CAD12862.1
CAD23613.1	CAD23614.1	BAH09387.1	AAD13644.1
AAD13651.1	AAD13652.1	AAB93837.1	AAB93839.1
2XV9_A	P46436.3	Q9UVU3	CAA06305.1
CAA73782.1	AAB07620.1	P79017.2	AAK49451.1
CAI78449.1	CAI78450.1	AAB95638.1	CAM54066.1
AAB60779.1	Q92450.3	O42799.2	CAB64688.1
Q4WB37.1	KEY81716.1	KEY78748.1	AAA32702.1
P12547.2	ADE74975.1	P29600.1	P00780.1
BAH10149.1	P04403.2	AAO38859.1	A45786
CAA96539.1	CAA96540.1	CAA96541.1	CAA96542.1
CAB02155.1	CAB02156.1	CAB02157.1	CAB02158.1
CAA05186.1	CAA05187.1	CAA05188.1	CAA05190.1
CAA07325.1	CAA07326.1	CAA07327.1	CAA07329.1
CAA04828.1	CAA04829.1	AAD26560.1	AAD26561.1
1LLT_A	AAB20452.1	CAA07328.1	CAA07320.1
4BKC_A	4BKD_A	4BK6_B	CAA33887.1
CAA54489.1	CAA54421.1	CAA54481.1	4BTZ_A
A4K9Z8.1	CAA55854.1	CAA60628.1	AAG22740.1
BAB21491.1	AAB25850.1	AAB25851.1	AJO53282.1
AAD13531.1	AAD13530.2	ABC68516.1	1YG9_A
ACY40651.1	AAA87851.1	ABP04043.1	ACJ37389.1
ABB89296.1	ABB89297.1	ABB89298.1	AAF72534.1
AAM83103.1	AAA78904.1	2MFK_A	AAC80579.1
AAX34047.1	AAM10779.1	AAQ24542.1	AAQ24543.1
APU87558.1	APU87557.1	APU87556.1	APU87554.1
Q7M4I6.1	Q7M4I3.1	P82971.1	P0CH88.1
AAA30478.1	NP_851372.1	ABW98943.1	ABW98945.1
AAB29137.1	AAA30433.1	NP_776719.1	Q28133.1
AAA30413.1	P02754.3	ACG59280.1	AAA51411.1
P80208.1	S65144	S65145	AAN86249.1
P69199.1	P81729.1	CAA57342.1	AAN11300.1
AAC48795.1	AAB30434.1	CAA76841.1	BAC10663.1
CCK33472.1	CAC34055.2	CAD10376.1	AAB02650.1
CAB02215.1	CAB02216.1	CAB02217.1	AAB20453.1
ABZ81041.1	AAB34907.1	AAB34908.1	AAB34909.1
AAO32314.1	ABW86978.1	ABW86979.1	ABV49590.1
ACJ23861.1	ACJ23863.1	CAA64868.1	ADN39439.1
BAA08246.1	Q7M1E7.1	BAF32143.1	AAF35431.1
A2V735.1	CAA09938.2	P02229.2	P02230.1
P84298.1	P12549.1	P12550.1	P02226.2
P02228.1	AAU43733.1	P84160.1	P84159.1
ABQ59329.1	CAQ72970.1	CAQ72971.1	CAQ72972.1
AGL34968.1	ADH10372.1	AGL34967.1	CAB39376.1
CAA96549.1	AAD48405.1	AAG40329.1	AAG40330.1
AAO65960.1	ACO56333.1	AAK01235.1	AAK01236.1
A4KA45.1	A4KA39.1	AAK28533.1	AAL73404.1
ACR43477.1	ACR43478.1	ACR43476.1	BAH10152.1
BAA05543.1	BAA05542.1	BAA07020.1	P43212.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

BAF32110.1	BAF32116.1	BAF32119.1	BAF32122.1
BAA06172.1	BAF45320.1	AAK27264.1	BAI94503.1
AAW69549.1	P83834.1	ACB45874.1	AAP13533.2
CAC05258.1	AAF72625.1	AAF72626.1	AAF72627.1
AAB28566.1	AAB28567.1	AAB32317.1	AAF80379.2
AAB50734.2	CAA69670.1	CAA01909.1	CAA01910.1
CAD20406.1	AAP96759.1	2103117A	CAA10345.1
AEY79726.1	AAB01092.1	BAA13604.1	CAB03715.1
ADL32660.1	ADL32661.1	ADL32662.1	ADL32663.1
AEY79728.1	AEY79727.1	CAA55072.2	CAA55067.2
AAX14379.1	P40918.1	CAD42710.1	ABA42918.1
AAD52672.1	AAM64112.1	AAP57094.1	ABU97470.1
AAP35082.1	AIO08851.1	AGC56218.1	AIO08848.1
BAX34757.1	BAE45865.1	AAP35068.1	ABO84970.1
BAC53948.1	ABA39436.1	ABU49605.1	AAP35075.1
ABL84751.1	BAA04557.1	AAK39511.1	AIO08864.1
AAL47677.1	CAI05850.1	CAI05849.1	CAI05848.1
BAA01239.1	ABN14313.1	AAA99805.1	ABY28115.1
ACK76296.1	ACK76297.1	AAF28423.1	AAP35077.1
ABO84964.1	ABO84966.1	ABO84967.1	ABO84968.1
AIP86946.1	AIP86945.1	AIP86944.1	AIP86943.1
AJF93907.1	AAP35080.1	AIO08867.1	AIO08866.1
ACD50950.1	ALA65345.1	AAG02250.1	CAD38361.1
CAD38366.1	CAD38367.1	CAD38368.1	CAD38369.1
ABV66255.1	3F5V_B	ACG58378.1	CAQ68250.1
AAB69424.1	CAA75141.1	ABB52642.1	ACI32128.1
CAD38372.1	CAD38373.1	CAD38374.1	CAD38375.1
CAD38381.1	CAD38382.1	CAD38383.1	ABA39437.1
AAF86462.1	CAQ68249.1	AFJ68070.1	AFJ68067.1
ALA22868.1	AAA19973.1	AAD38942.1	P49274.1
AAA80264.1	CAC09234.1	AAB35977.1	AAB32224.1
P53357.1	CAA47341.1	AAA68279.1	AAA28301.1
P81217.1	CAA52194.1	AAM09530.3	BAF47268.1
BAF76430.1	AAC82351.1	AAC82352.1	AAC82350.1
BAO50872.1	BAO50870.1	AAX57578.1	ABC18306.1
BAT21117.1	ABO93594.1	ADW27428.1	ABI32184.1
CAA44343.1	CAA44344.1	P30438.2	AAC37318.1
AAL49391.1	AAS77253.1	ADK56160.1	ADM15668.1
ACD65080.1	ACD65081.1	CAJ85646.1	CAJ85644.1
ACX47058.1	4C9C_B	CAC86258.1	AAY83342.1
AAQ83588.1	AAV74343.1	AAQ08947.1	BAH10153.1
P02622.1	AAK63086.1	AAK63087.1	CAM56785.1
P01005.1	ACJ04729.1	CAA23681.1	P01012.2
P02789.2	P00698.1	AAA48944.1	CAA23711.1
ADD18879.1	ADD19985.1	ADD19989.1	AAF82096.1
CAA11756.1	CAA42646.1	CAA35691.1	AAA33947.1
BAB64306.1	P25974.1	CAA26723.1	AAA33966.1
CAA26478.1	BAA74953.1	AAA33964.1	AAA33965.1
ACD36975.1	ACD36974.1	ACD36978.1	BAB21619.2
CAA45777.1	CAA45778.1	AAB23464.1	AAB23482.1
CAB76459.1	AAQ54603.1	BAH10148.1	BAJ61596.1
P23110.1	CAB38044.1	CAA39880.1	AAA16792.1
AAP37470.1	ADR82196.1	CCW27997.1	AAA87456.1
ABN09654.1	ABN09655.1	ACY91851.1	ACZ74626.1
AAR98518.1	AAC49447.1	CAA05978.1	1WKX_A
AAF25553.1	CAE85467.1	CAA75312.1	1G5U_A
CAB96215.1	CAC00532.1	Q9LEI9.1	CAD24068.1
CAB10766.1	CAB10765.1	AAG42255.1	AAC48288.1
CAA42832.1	AAA32970.1	CAA35188.1	CAA08836.1
AAP94213.1	AAP15200.1	AAP15199.1	AAM54365.1
ACI47547.1	AAW29810.1	CAC05582.1	P81295.1
AAR21071.1	Q9LD79.2	AAF80164.1	AAF80166.1
CAD87731.1	AAQ55550.1	CAB71342.1	CAB62213.1
AAQ73484.1	AAQ73486.1	AAQ73487.1	AAQ73488.1
CAA57160.1	CAA58755.1	AAQ73493.1	AAQ73494.1
CAC84593.2	CAA54818.1	CAA54819.1	AAZ91659.1
ACM89179.1	ACB38288.1	ABI98020.1	ACC76803.1
Q7M1X5.1	P14947.1	CAA51775.1	P14948.1
Q40240.2	CAI84850.2	Q53HY0.2	Q6EBC1.1
F5B8W4.1	F5B8W3.1	F5B8W2.1	F5B8W1.1
AHA85706.1	P86739.1	P86741.1	P86740.1
CAA65341.1	CAD20981.3	CAD68071.1	CAI43283.4
CAA09887.4	CCU97864.1	CCV00099.1	CCU98198.1
CAA96535.1	CAA96536.1	CAA96537.1	AAD13683.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

AAD26553.1	AAD26554.1	AAD26555.1	AAD26558.1
CAA88833.1	CAA58646.1	AAK13029.1	AAK13030.1
Q9FSG7.1	CAT99612.1	CAT99611.1	AFM77001.1
AAT80662.1	AAT80659.1	AAT80649.1	AAR22488.1
AAX19854.1	AAX19856.1	AAX19858.1	AAX19860.1
CAT99619.1	CAT99617.1	AAD29412.1	AAD29413.1
B3EWE5.3	G5DC91.2	BAF47263.1	AGF86397.1
P86752.1	P86753.1	P86754.1	P86757.1
P86768.1	P86769.1	P86770.1	P86771.1
Q99MG7.1	AAA60330.1	AAG08989.1	AHW81906.1
CAA26953.1	A2BIM8.1	AAA39768.1	AAK54834.1
BAD36780.1	AAB50883.1	CAA49760.1	2206305A
BAE54433.1	P19963.2	I53806	E53806
B53806	H53806	CAA73038.1	CAA73037.1
AAN18044.1	AAQ10281.1	AAQ10280.1	AAQ10279.1
AAQ10271.1	AAQ10268.1	AAQ08190.1	ABP58632.1
AAL92578.1	AAY88919.1	ACZ57582.1	E1U332.1
A4GFC3.1	CAA73035.1	AAD05375.1	AAO33897.1
ABX26132.1	ABX26134.1	ABX26138.1	ABX26139.1
ABX26147.1	ABX54842.1	ABX54844.1	ABX54849.1
ABX54866.1	ABX54869.1	ABX54876.1	ABX54877.1
AAK58515.1	2JON_A	BAE54432.1	Q25632.1
AFV53352.1	AAG42806.1	AAG42802.1	Q948T6.2
BAD13150.1	BAC20657.1	BAA01998.1	BAA01996.1
BAA07711.1	BAA07712.1	BAA07713.1	AAB99797.1
ADK39021.1	ACA96507.1	CBY17558.1	AAC38996.1
CAA54587.1	CAI94601.1	CAA59370.1	CAA65122.1
CAP05019.1	Q7M1E8	AAB36008.1	AAB36009.1
AAB46819.1	AKF12278.1	CBM42667.1	CBM42666.1
CBM42661.1	CBM42660.1	ACA23876.1	AAX37288.1
AAX11194.1	AAF71379.1	AAG44693.2	AAF23726.1
AAG44480.1	Q92260.1	AAK51201.1	AAR17475.1
AEX34122.1	AAG44478.1	AKH04310.1	AKH04311.1
ACS14052.1	AAC34736.1	AAC34737.1	AAB82404.1
AAX33734.1	AAX33727.1	ADR82198.1	AAB09632.1
ADD17628.1	AAX33728.1	3EBW_A	ACJ37391.1
AAG08988.1	CAB01591.1	AAB27445.1	Q41260.1
ADC80502.1	ADC80503.1	CAA55390.1	CAA81613.1
CAA70609.1	ABG81289.1	ABG81290.1	ABG81291.1
CAA70608.1	CAA54686.1	CAB42886.1	CAA53529.1
CAQ55939.1	CAQ55940.1	CAQ55941.1	3TSH_A
Q7M1L8	2023228A	CAB05371.1	CAB05372.1
AAC16528.1	AAC25994.1	AAC25995.1	AAC25997.1
CAD38386.1	CAD38387.1	CAD38388.1	CAD38389.1
CAD38394.1	CAD38395.1	CAD38396.1	CAD38397.1
CAA76556.1	CAA76557.1	CAA76558.1	1NLX_N
AHC94918.1	CEJ95862.1	CTQ87571.1	ABU42022.1
ABR29644.1	CAF25233.1	CAF25232.1	CAB82855.1
CAC41633.1	CAC41634.1	CAC41635.1	CAD80019.1
CAD20556.1	CAE52833.1	CAC85911.1	CBW45298.1
P22284.1	P22286.1	A60373	P22285.1
AAS67044.1	AAS67043.1	AAS67042.1	AAS67041.1
P83542.1	A2VBC4.1	ADT89774.1	ADL09135.1
P05946.1	AGE44125.1	ABL89183.1	ABS12234.1
BAH59276.1	AAB97141.1	ADR66945.1	ADR66946.1
AAS47036.1	AAS47035.1	1H2O_A	AAF26449.1
P82534.1	ACE80974.1	AAL91662.1	3EHK_A
ACE80939.1	ACE80956.1	ACE80958.1	ACE80957.1
P83335.1	AEV57471.1	ABB78006.1	AJE61291.1
AGW21344.1	CAD37201.1	CAD37202.1	P86888.1
AHB19225.1	AAF26451.1	AET05733.1	AET05732.1
ABZ81045.1	ABZ81047.1	ABZ81046.1	CAC83046.1
Q63213	AAA41198.1	AIS82657.1	AAP30720.1
Q91483.3	ACI68103.1	CAA66403.1	CBL79146.1
ARS33724.1	AAT99258.1	AAX11261.1	AAX11262.1
AHL24658.1	ADK22841.1	ADK22842.1	CAX32966.1
AAS93674.1	AAS93675.1	AAS93676.1	AAO15607.1
Q7M1Y1	C37396	D37396	AAP06493.1
BAW32536.1	BAW32535.1	BAC66618.1	CAX32965.1
CAQ72969.1	AAB37403.1	AAB37406.1	AAB34365.1
BAE54429.1	BAE54430.1	ACB55491.1	AAK15088.1
ACH85188.1	AAD42942.1	AAD42944.1	AAK15087.1
CAA62908.1	P15322.2	AAX77383.1	AAX77384.1
NP_001316123.1	CAD10377.1	AAL29690.1	AAL75449.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

AHC08074.1	AHC08073.1	ABA81885.1	ABB16985.1
P15476.2	P16348.1	P20347.3	AAB63099.1
AAC97370.1	AAC97369.1	AAB36117.1	AAB36119.1
AAB65434.1	P35776.2	P35779.2	ADD74392.1
AIL01320.1	AIL01321.1	ACT37324.1	1ESF_B
AAT66567.1	ABS29033.1	AAT66566.1	AAD46493.1
P58171.1	S43242	S43243	S43244
P86360.1	CEE03319.1	CEE03318.1	AAK63089.1
P86979.1	BAE54431.1	BAE46763.1	BAH10155.1
CAD23374.1	P24296.2	CAA42453.1	ACG59281.1
AKJ77990.1	AKJ77985.1	CAA35238.1	CAA25593.1
AAA34276.1	AAA34279.1	AAA34280.1	AAA34281.1
P81496.1	ACE82289.1	BAE20328.1	CAR82265.1
CAI64396.1	P08819.2	P27357.1	ACE82291.1
CBA13560.1	AAA34272.1	AAA34274.1	AAA34288.1
CAY54134.1	CAB96931.1	CAA43331.1	CAA31396.1
CAA27052.1	CAA24933.1	BAN29068.1	CAA31395.4
CAZ76052.1	CBA13559.1	CAA35597.1	CAC14917.1
CAZ76054.1	CAA31685.1	CAA30570.1	AAA34285.1
CAA59339.1	CAA59340.1	O22108	CAI79052.1
P82977.2	CCK33471.1	APY24042.1	CAA34709.1
AAX34057.1	AAX34058.1	AAX34059.1	AOD75395.1
AAT40866.1	AAU11502.1	ABM53751.1	ABU97480.1
AAT66607.1	AAT66609.1	ACH42744.1	AAT66610.1
ABQ59259.1	ABQ59258.1	ABQ59255.1	ACJ54737.1
BAH10157.1	P0DMB5.1	P0DMB4.1	P0CH87.1
P81657.1	P35783.1	CAJ28931.1	P35784.1
P35760.1	ABC73068.1	P0CH89.1	P35785.1
AAA30333.1	CAB42887.1	1QNX_A	P49370.1
ABG02262.1	ABW23574.1	BAA74451.1	CAA50008.1
ABD79096.1	ABD79097.1	ABD79098.1	ACX37090.1
AAK56124.1	2HCZ_X	ABD79094.1	ABD79095.1
AAB86960.1	ABG81312.1	ABG81313.1	ABG81314.1
CAA51718.1	CAA51719.1	CAA51720.1	AAG35601.1
AAX40948.1			

M5ECN9.1	P38948.1	P00709.1	P79085.1
P42058.1	P0C0Y4.1	P27759.1	Q2KN25.1
P10414.1	Q8L5L5.1	Q8GZP6.1	Q8H2B8.1
P00630.1	P43238.1	Q45W87.1	Q6PSU2.1
H6VGI3.1	Q84ZX5.1	A0PJ16.1	P67875.1
Q4WWX5.1	O60024.1	Q92450.1	Q09072.1
P43187.1	Q39419.1	O65002.1	P05814.1
P54962.1	O18598.1	Q1A7B3.1	Q9NG56.1
P02663.1	P02666.1	P02668.1	Q28133.1
O18873.1	P49822.1	P09582.1	B5KVH4.1
P02229.1	Q7XCK6.1	P40108.1	P42039.1
Q6IQX2.1	P20023.1	Q08407.1	Q8S4P9.1
Q9SCG9.1	Q9M4S6.1	Q69CS2.1	Q96VP3.1
Q7M1X8.1	Q41183.1	P93124.1	P82946.1
Q1M2P5.1	Q94507.1	Q8MVU3.1	Q86R84.1
Q8N0N0.1	P49278.1	Q2L7C5.1	P39675.1
Q9UL01.1	O15315.1	P11388.1	P30575.1
Q2PS07.1	P49327.1	P30438.1	Q5VFH6.1
P01012.1	P19121.1	P02230.1	P02224.1
P04776.1	P04347.1	P04405.1	P08238.1
O82803.1	Q39967.1	P02877.1	P62805.1
P93198.1	Q9SEW4.1	Q2TPW5.1	P81294.1
P80384.1	P31025.1	Q004B5.1	P14946.1
Q40237.1	P14174.1	Q5H786.1	P30440.1
Q16655.1	Q07932.1	Q9ZNZ4.1	Q9H009.1
Q8NFH4.1	P19963.1	Q94G86.1	P01014.1
O75475.1	O24554.1	Q0IX90.1	Q52PJ2.1
A1KYZ2.1	P23284.1	Q9TZR6.1	Q25641.1
Q8H6L7.1	P35079.1	Q9XG86.1	P43214.1
Q8L5D8.1	P82242.1	Q9HCM2.1	Q9ZP03.1
P25788.1	P81651.1	O24248.1	P82534.1
P67876.1	Q9Y4W2.1	Q9ULX3.1	P83181.1
P15322.1	Q15020.1	B9SA35.1	P01267.1
Q7M3Y8.1	P25445.1	Q5NT95.1	P07101.1
Q8W3V4.1	P49370.1	Q05110.1	Q9ULJ6.1
AGC39173.1	AGC39174.1	P00785.4	P85204.1
AGC39176.1	CAA34486.1	AAA32629.1	A5HII1.1
CAI38795.2	ABQ42566.1	AAR92223.1	P84527.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

4X9U_B	AGC39169.1	AGC39170.1	AGC39171.1
AAB58417.1	ABF18122.1	XP_001653462.1	XP_001654143.1
P13080.1	E37396	Q7M1X7	Q7M1X9
AAS75297.1	3V0R_A	4AUD_B	CAA55071.2
AAB48041.1	P42037.1	Q9HDT3.2	P42058.1
CAD38167.1	ABI26088.1	ACP43298.1	AKV72168.1
AAA32669.1	CBW30986.1	CBW30987.1	CBW30988.1
CBW30993.1	CBW30994.1	CBW30995.1	AAX77686.1
CBK62694.1	CBK62695.1	CBK62697.1	CBK62698.1
AAP15201.1	AAX77687.1	AAX77688.1	5EM1_A
5EGW_B	P00304.2	P02878.1	AAA20065.1
P10414.2	AEK65120.1	AAM73729.1	AAM73730.2
CDZ09832.1	AGC60026.1	AGC60027.1	AGC60028.1
ACZ95445.1	BAJ78220.1	BAJ78221.1	BAJ78222.1
BAT62430.1	AAF75225.1	Q9NJA9.1	Q9NAS5.1
ABL77410.1	BAF75681.1	BAF75704.1	BAF75705.1
BAF75710.1	BAF75711.1	BAF75712.1	ABV55106.1
A59055	AAK09361.1	Q7M4I5.1	P01502.1
ACI25605.1	Q5BLY5.1	CAA26038.1	MEHB2
AAY21180.1	CAD56944.1	AHM25038.1	AHM25037.1
ACV04796.1	AAD29409.1	P81943.3	P86809.1
AAT00594.1	AAT00596.1	ADQ53858.1	3SMH_A
AAN77576.1	AAM78596.1	AAK96887.1	ACN62248.1
ABI17154.1	ACH91862.1	3C3V_A	ADQ53859.1
AAL37561.1	1W2Q_A	Q647G9.1	AAD56719.1
ABG85155.1	ABX56711.1	ABX75045.1	AAU21499.2
2X45_A	AHF71021.1	AHF71022.1	AHF71023.1
CAK50834.1	P0C088.1	ACE07186.1	ACE07187.1
5EM0_A	AAX85388.1	AAX85389.1	CAD23611.1
AAD13645.1	AAD13647.1	AAD13649.1	AAD13650.1
AAD13646.1	ACN32322.1	AAB26195.1	Q06811.2
AAF86369.1	P67875.1	CAA59419.1	CAB44442.1
Q96X30.3	AAM43909.1	Q8NKF4.2	CAI78448.1
CAA04959.1	O60024.2	CAA83015.1	P46075.3
Q9UUZ6.2	CAA11266.1	Q875I9.1	EAL89830.1
CAB06417.1	AAD13106.1	P0C1B3.1	AAA32708.1
AAG31026.1	BAA05540.1	BAF46896.1	AIV43661.1
CAA54696.1	CAA54695.1	CAA54694.1	CAA96546.1
CAA96543.1	CAA96544.1	CAA96547.1	P43186.2
CAB02159.1	CAB02160.1	CAB02161.1	CAA96545.1
CAA07318.1	CAA07319.1	CAA07323.1	CAA07324.1
CAA07330.1	CAA04823.1	CAA04826.1	CAA04827.1
AAD26562.1	P43180.2	1QMR_A	AAP37482.1
CAA54488.1	1B6F_A	4BK7_A	4B9R_A
CAA54482.1	CAA54483.1	CAA54484.1	CAA54487.1
4Z3L_D	B45786	1CQA_A	AAA16522.1
CAC84116.1	AHF71027.1	BAB21489.1	BAB21490.1
AAB29344.1	AAB29345.1	ACM24358.1	ABC86902.1
ABP35603.1	AAA86744.1	3LIZ_A	ACY40650.1
ACF53836.1	ACF53837.1	ABP04044.1	AAB72147.1
ABX57814.1	AAK58415.1	AAQ24541.1	ABU97466.1
ABH06350.1	ABH06347.1	ABH06346.1	ABH06348.1
AAD10850.1	ABH06352.1	ABH06359.1	2JMH_A
AAQ24545.1	ASX95438.1	AAP35069.1	ACV04860.1
ABB88514.1	XP_005902099.2	AAA62707.1	AAA30429.1
ABW98953.1	NP_776953.1	AAA30430.1	AAA30431.1
Q28050.1	CAA29664.1	AAA30615.1	CAA32835.1
CAA76847.1	NP_776945.1	NP_851341.1	P80207.1
XP_013623213.1	S65143	CAA46782.1	BAA09634.1
P30575.1	AAC48794.1	CAD82911.1	CAD82912.1
ACY38525.1	AHY24648.1	CAA68720.1	CCF72371.1
CAA47357.1	CAB02206.1	CAB02207.1	CAB02208.1
ABZ81044.1	ABZ81040.1	ABZ81043.1	ABZ81042.1
CAA47366.1	CAB02209.1	CAB02213.1	CAA47367.1
5E1R_F	ABM53030.1	CAD10374.1	ACJ23862.1
2MC9_A	P83507.1	CAX62129.1	CAX62130.1
AAL07319.1	AAL92870.1	ACR77509.1	AAL92871.1
P02221.2	P84296.1	P02227.1	P12548.1
P02222.2	P02223.2	P02224.2	P02231.1
CAI23765.1	P84161.1	CAH03799.1	ADK47394.1
AAK67491.1	AAK67492.1	ACF19589.1	ABC88428.1
CAA50325.1	CAA50326.1	CAA50328.1	CAA96548.1
AAG40331.1	CAA50327.1	AAL86739.1	AAO67349.2
A4KA41.1	A4KA40.1	A4KA44.1	A4KA43.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

AHA36627.1	ACR43473.1	ACR43474.1	ACR43475.1
ARX70262.1	AAC61869.1	AAW81034.1	BAD77932.1
BAC23082.1	BAC23083.1	BAC23084.1	BAF32105.1
BAF32128.1	BAF32130.1	BAF32133.1	BAF32134.1
BAJ04354.1	BAF51970.1	BAA06905.1	CAD92666.1
CAB62551.1	CAC37790.2	ABK78766.1	ACY01951.1
AAF72628.1	AAF72629.1	AAR21074.1	AAR21073.1
AAK96255.1	AAL14077.1	AAL14078.1	AAL14079.1
CAA62634.1	AAS02108.1	CAC83658.1	CAC83659.1
AAB42200.1	P82946.1	AAK62278.1	CAD20405.1
CAB03716.1	CAB06416.1	AAL76932.1	BAB88129.1
ADL32664.1	ADL32665.1	ADL32666.1	AAL76933.1
CAA55070.1	P42040.2	CAA55068.1	AAO91801.1
CAD38166.1	ATI08931.1	L7UZ85.1	AAP35078.1
AIO08850.1	AGI78542.1	AGC56216.1	AIO08860.1
AAP35065.1	AGC56219.1	AIO08870.1	AIO08861.1
ABO84971.1	ABO84972.1	ABO84973.1	P16311.2
AFJ68066.1	ADM52184.1	ABL84749.1	ABL84750.1
P39673.1	BAA04558.1	BAA01240.1	BAA01241.1
ABA39438.1	BAD74060.2	AAP35073.1	AFJ68072.1
ACK76291.1	ACK76292.1	BAA09920.1	AAB27594.1
ACK76299.1	AIO08853.1	AAM19082.1	ABO84963.1
ABO84969.1	AHC94806.1	BAV90601.1	AHX03180.1
AIP86942.1	AIP86941.1	AIP86940.1	AIP86939.1
P16312.1	ATI08932.1	AAY84565.1	AAY84564.2
CAD38362.1	CAD38363.1	CAD38364.1	CAD38365.1
CAD38370.1	CAD38371.1	AAX47076.1	2AS8_B
AAA28296.1	AAB60215.1	AFJ68065.1	ABA39435.1
AAO73464.1	ADK92390.1	AAM21322.1	1KTJ_A
CAD38376.1	CAD38377.1	CAD38378.1	CAD38379.1
CAK22338.1	ABG76196.1	1A9V_A	ABY53034.1
ABC73706.1	ACB46292.1	4ZCE_A	ALA22869.1
AAB32842.1	CAD69036.1	CAA35692.1	P49277.1
AAX37326.1	AAY84563.1	ABC96702.1	AAA28303.1
AAA28302.1	P83340.1	AAC48691.1	P81216.1
BAF47269.1	AAO73305.1	ABO71783.1	BAF76431.1
AAC82349.1	BAK09233.1	BAK09232.1	BAB79444.1
O23878.1	O23880.1	Q9XFM4.1	ABQ10638.1
ACJ23865.1	ACJ23864.1	ACJ23866.1	AAZ76743.1
NP_001041618.1	CAA44345.1	AAC41616.1	CAA59279.1
AAS98889.1	AAS98890.1	AGT20779.1	AEM89226.1
CAJ85642.1	CAJ85641.1	ABD39049.1	ACX47057.1
AAY83341.1	AAY83345.1	AHL24661.1	AHL24660.1
AAN73248.1	AAL79930.1	AAL79931.1	AHY02994.1
CAM56786.1	B3A0L6.1	P86980.1	NP_990450.1
CAA23682.1	1JTI_A	1UHG_D	CAA26040.1
CAA43098.1	BAA13973.1	P02604.3	CAX32963.1
ACS49840.1	P24337.1	CAA11755.1	ABU97472.1
BAA23360.2	AAB01374.1	BAB64303.1	BAA74452.2
CAA26575.1	BAA00154.1	CAA33217.1	CAA37044.1
BAB15802.1	AAD09630.1	NP_001238443.1	ACD36976.1
P22895.1	AAB09252.1	BAA25899.1	P82947.1
AAB23483.1	CAA56343.1	CAA60533.1	CAB59976.1
AAG08987.1	APG42675.1	CAA75506.1	AAP47226.1
CAB53458.1	CAC13961.1	CAC42881.1	AAL25839.1
AAP87281.1	ABN03965.1	ABN03966.1	ABN09653.1
AEV41413.1	AFJ97275.1	AFJ97274.1	AAC82355.1
ABW34946.1	AAC27724.1	CAA11041.1	CAA11042.1
AAF34341.1	AAF34342.1	AAF34343.1	CAB51914.1
CAA81610.1	CAA93121.1	CAA10140.1	Q7M262
AAC48287.1	P32936.2	P80198.1	CAA51204.1
CAA41956.1	CAA49555.1	CAA45085.1	CAA46705.1
AAM54366.1	APR62629.1	AAB41308.1	AAF18269.1
AAD03608.1	CAC48400.1	AAC15474.2	AAR21072.1
AAV97933.1	AAT45383.1	AAX35807.1	CAD87730.1
CAD32313.1	CAD32314.1	2118249B	2118249A
AAQ73489.1	AAQ73490.1	AAQ73491.1	AAQ73492.1
CAB62212.1	CAB65963.1	CAP17694.1	CAC84590.2
BAW03243.1	BAW03242.1	AAL07320.1	ABC02750.1
P14946.2	AAA63278.1	AAA63279.1	CAB63699.1
CAH92637.1	AAD20386.1	CAB64344.1	AAA33405.1
ABR21771.1	ABR21772.1	ACB05815.1	F5B8W5.1
F5B8W0.1	F5B8V9.1	B3A0N2.1	ADC55380.1
P86742.1	BAA32435.1	BAA32436.1	AAD25927.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

CAA09883.1	CAA09884.1	CAA09885.1	CAA09886.2
CCU99457.1	SHO79205.1	CCU99206.1	CAA96534.1
AAD26546.1	AAD26547.1	AAD26548.1	AAD26552.1
CAD32318.1	AAO25113.1	AAD29671.1	AAB01362.1
AAK13027.1	AAB35897.1	AAX19848.1	AAX19851.1
AAC36740.1	O29330.1	AAT80665.1	AAT80664.1
Q9M5X7.1	CAD46559.1	CAD46561.1	CAD46560.1
CAK93713.1	CAK93753.1	CAK93757.1	CAT99618.1
AAD29414.1	AAM55492.1	AEE98392.1	B3EWS0.1
CAA73720.1	P86745.1	P86749.1	P86750.1
P86761.1	P86760.1	P02620.1	P86765.1
P86772.1	P86774.1	P86775.1	AAD55792.2
AAV33670.1	AAV33672.1	P85894.1	P02762.2
2CYG_A	1Z3Q_A	CAC81811.1	AAB82772.2
AAB36316.1	BAH10150.1	CAE17317.1	CAE17316.1
F53806	C53806	A38968	G53806
CAA73036.1	AAB32652.2	AAO22133.1	AAO22132.1
AAQ10278.1	AAQ10277.1	AAQ10276.1	AAQ10274.1
ABP58633.1	ABP58635.1	ABP58636.1	ABP58637.1
E3SU11.1	O24170.1	O24171.1	A4GFC0.1
P80740.2	CAD21706.2	ABP58627.1	ABX26131.1
ABX26140.1	ABX26141.1	ABX26143.1	ABX26145.1
ABX54855.1	ABX54859.1	ABX54862.1	ABX54864.1
AAB66909.1	P81430.2	AAF31152.1	AAF31151.1
BAJ07603.1	P86431.1	P86432.1	BAF95206.1
AAA86533.1	AAF72991.1	BAB71741.1	Q40638.2
BAA07772.1	BAA07773.1	BAA07774.1	BAA07710.1
Q01882.2	Q01883.2	BAC19997.1	BAC20650.1
BAF47265.1	BAF47266.1	2008179A	CAA65123.1
P55958.1	Q9T0M8.1	Q9XG85.1	CCP19647.1
AAB36010.1	AAB36011.1	AAB36012.1	AAB46820.1
CBM42665.1	CBM42664.1	CBM42663.1	CBM42662.1
AAO15713.1	C7E3T4.1	ADV17342.1	ADV17343.1
AAM33821.1	AAB34785.1	ADK27483.1	AAD25995.1
AAD42074.1	ABB89950.1	ABM60783.1	AAD25926.1
AAX33729.1	AEV23867.1	AAD19606.1	CAB38086.1
AAC34312.1	AAD13533.1	AAP13554.1	ADB92492.1
AAB62731.1	AAB63595.1	Q25641.1	ADB92493.1
AAX33730.1	AAT77152.1	ACA00204.1	AAL86701.1
P56164.1	P56165.1	P56166.1	P56167.1
1N10_A	CAG24374.1	2118271A	AAN32987.1
ABG81292.1	ABG81293.1	ABG81294.1	ABG81295.1
CAD54670.2	CAF32567.2	CAF32566.2	CAQ55938.1
CAD54671.2	CAA52753.1	S32101	S38584
CAA50281.1	AAC16525.1	AAC16526.1	AAC16527.1
AAC25998.1	AAK25823.1	CAD38384.1	CAD38385.1
CAD38390.1	CAD38391.1	CAD38392.1	CAD38393.1
1L3P_A	CAD87529.1	CAA81609.1	CCD28287.1
CAA76887.1	3FT1_A	AGT28425.1	CAD10390.1
ABG73109.1	ABG73110.1	ABG73108.1	ABO36677.1
AJG44053.1	A0A158V755.1	A0A158V976.1	2N81_A
ABY21305.1	ABY21306.1	ALF39466.1	ALF00099.1
A60372	F37396	CAA10520.1	AAG42254.1
AAA29793.1	AAD52615.1	AAD52616.1	AAT95010.1
AAP37412.1	AAT95009.1	P35780.1	P83377.1
P86687.1	ADD63684.1	P86686.1	Q7Z156.2
AFA45339.1	ACN87223.1	AKV72167.1	AHY24177.1
ADR66947.1	ADR66948.1	AAC02632.1	AAS47037.1
ADR66943.1	ADR66944.1	AAD29411.1	AAB38064.1
AGR27935.1	ADN39440.1	ADN39441.1	P82952.1
ACE80959.1	ACE80955.1	ACE80972.1	P83332.1
AJE61290.1	P81402.1	AAV40850.1	ADR66939.1
BAH10154.1	C0HKC0.1	AHB19227.1	AHB19226.1
AET05730.1	O65200.1	AAD29410.1	AAC24001.1
CAC95152.1	CAC83047.1	CAC95153.1	P02761.1
AAT37679.1	CAA38097.1	ABG54495.1	ABG54494.1
ACH70931.1	CBL79147.1	NP_001133181.1	AHL24657.1
ACO34813.1	P83181.1	ACO34814.1	ACS34771.1
CAX32967.1	SHD75397.1	AAO15613.1	AAS93669.1
AAX37321.1	AGM48615.1	CAQ68366.1	BAH10151.1
AAC67308.1	XP_003030591.1	BAW32538.1	BAW32537.1
AFA45340.1	AFJ80778.1	ABS12233.1	CAQ72968.1
CAH92630.1	CAH92627.1	Q7M263	CBG76811.1
ACI41244.1	AAD42943.1	AAK15089.1	AAG23840.1

TABLE 6-continued

LIST OF ACCESSION NUMBERS FOR ALLERGENS FROM IEDB & ALLERGENONLINE

CAA62909.1	CAA62910.1	CAA62911.1	CAA62912.1
ABU95411.1	ABU95412.1	ABU53681.1	NP_001306883.1
AAL75450.1	CAJ19705.1	AAB42069.1	CAA75803.1
CAA31575.1	CAA27571.1	CAA27588.1	AAA33819.1
BAA04149.1	BAH10156.1	AAF65312.1	AAF65313.1
AAB36120.1	AAB36121.1	AAT95008.1	P35775.1
AIL01319.1	AIL01318.1	AIL01316.1	AIL01317.1
CAJ43561.1	P34071.1	P20723.1	P06886.1
AAS75831.1	P00791.3	AAA30988.1	NP_001005208.1
ADX78255.1	ADM18346.1	ADM18345.1	ADK47876.1
AAK63088.1	CBL79145.1	P86978.1	CAX62602.1
AAF07903.2	AAD52013.1	AAD52012.1	Q8J077.1
AKJ77988.1	AKJ77986.1	AKJ77987.1	CAI64398.1
CAA26383.1	CAA26384.1	CAA26385.1	AAA34275.1
AAA34282.1	AAA34283.1	AAA34284.1	BAA12318.1
CAR82266.1	CAR82267.1	BAN29067.1	CAI64397.1
CAA61945.2	CAA61943.2	CAA61944.2	CAQ57979.1
AAA34289.1	BAA11251.1	CAI78902.1	BAN29066.1
CAA26847.1	CAA24934.1	CAA43361.1	AAB02788.1
AAZ23584.1	BAC76688.1	CAI84642.1	CAA35598.1
ACE82290.1	Q6W8Q2.1	CAA72273.1	CAB52710.1
AAA34286.1	AAA34287.1	O22116	CAA59338.1
AEH31546.1	BAN29069.1	CAA65313.1	ABS58503.1
CAA39099.1	CAA36063.1	CAA44473.1	AAA34290.1
AOD75396.1	AOD75399.1	ABQ96644.1	ABU97479.1
CAA73221.1	ACL36923.1	ABZ81991.1	AGG10560.1
ACJ65836.1	AGC36415.1	ACH42743.1	ACI44002.1
ACH42741.1	AGC36416.1	AKV72166.1	AIV43662.1
P35781.1	P35782.1	CBY83816.1	CBY93636.1
CAJ28930.1	CAL59818.1	CAL59819.1	P51528.1
P35786.1	P0CH86.1	P35787.1	AAB48072.1
CAI77218.1	2ATM_A	ACA00159.1	AAX19889.1
P80273.2	P80274.1	P33556.1	CAR48256.1
P29022.1	2209273A	AAO45607.1	AAO45608.1
ABF81661.1	ABF81662.1	Q1ZYQ8.2	P0C1Y5.1
ABG81315.1	ABG81316.1	ABG81317.1	ABG81318.1
5FEF_A	AAA33493.1	AAA33494.1	CAI64400.1

TABLE 7

LIST OF ACCESSION NUMBERS FOR AUTOMIMMUNE ANTIGENS FROM IEDB

	I7HKY1.1	Q9P0J1.1	P61604.1	Q9NUQ2.1	Q9P212.1	P16885.1	P09543.1
P17980.1	Q99460.1	O00231.1	O00487.1	P48556.1	Q61733.1	P82909.1	P21953.1
Q9CHK3.1	Q9BYD6.1	Q9BYC9.1	Q96A35.1	Q9P0J6.1	P04035.1	Q99714.1	B2RLH8.1
P62277.1	P08708.1	P62269.1	P63220.1	P62851.1	P62273.1	P62861.1	P46781.1
P08865.1	P17643.1	Q9H0D6.1	F5HCM1.1	E5RK45.1	A0A0B7JKK9.1	A1JIP3.1	B2RKS6.1
P0A6F5.1	P0C0Z7.1	Q49375.1	Q9Z708.1	P0A521.1	P42384.1	P0A520.1	P9WPE7.1
P10809.1	P10155.1	P05388.1	P05386.1	P05387.1	P27635.1	P62906.1	P40429.1
P35268.1	A8MUS3.1	P62750.1	P61353.1	P46776.1	P46779.1	P47914.1	P39023.1
P62888.1	Q02878.1	P18124.1	P62917.1	P32969.1	Q6SW59.1	P08253.1	P11021.1
Q969T7.1	Q76LX8.1	C6AV76.1	Q2FWL5.1	B1RDC1.1	Q2G2D8.1	P42684.1	Q8IZT6.1
Q9Y4K1.1	P02709.1	P02710.1	P02711.1	P04756.1	P02708.1	P02712.1	P11230.1
Q07001.1	P02715.1	Q04844.1	P07510.1	P13536.1	F1N690.1	M9YGB9.1	O43427.1
P68133.1	P62736.1	P60709.1	P63261.1	Q9NQW6.1	O15144.1	Q9H981.1	Q8N3C0.1
Q6VMQ6.1	Q6JQN1.1	Q5T8D3.1	P82987.1	Q6ZMM2.1	Q9NZK5.1	Q8IUX7.1	Q9NP61.1
Q9UJY4.1	O43488.1	P07897.1	P16112.1	Q73ZL3.1	Q92667.1	P49588.1	C9JKR2.1
F8ELD9.1	P15121.1	F5HF49.1	P05186.1	P55008.1	Q5STX8.1	P02763.1	P01009.1
P35368.1	P04217.1	P25100.1	P08697.1	P18825.1	P02765.1	P01023.1	P12814.1
O43707.1	P35611.1	Q9UBT7.1	P61163.1	P02489.1	P02511.1	P06733.1	P06280.1
Q16352.1	Q96Q83.1	P37840.1	Q9UJX4.1	P01019.1	Q9P2G1.1	Q9H8Y5.1	Q8N6D5.1
H0YKS4.1	P04083.1	P50995.1	P07355.1	P08758.1	P08133.1	Q9NQ90.1	Q03518.1
P01008.1	Q10567.1	Q9BXS5.1	Q96CW1.1	O00203.1	P02647.1	P02652.1	P06727.1
P04114.1	P02655.1	C9JX71.1	P05090.1	P02649.1	Q9BZR8.1	P03182.1	Q9BRQ8.1
Q9ATL6.1	P47863.1	P55087.1	P55064.1	P20292.1	Q15057.1	Q96P48.1	P35869.1
Q5VUY2.1	P03928.1	P25705.1	P06576.1	P56385.1	Q9DB20.1	P18859.1	Q9BZC7.1
Q8WWZ7.1	Q9NUT2.1	P61221.1	P53396.1	A1JNN2.1	P0A6G7.1	Q9H2U1.1	Q14562.1
O84848.1	P78508.1	Q99712.1	P17342.1	Q99856.1	Q8IVW6.1	Q96GD4.1	Q8WXX7.1
O15392.1	P02730.1	P98160.1	F8W034.1	P20749.1	P41182.1	Q9NYF8.1	Q6W2J9.1
Q8NFU0.1	P15291.1	P07550.1	P02749.1	P61769.1	Q13425.1	Q562R1.1	P42025.1
P13929.1	F0K2P6.1	O43252.1	Q13057.1	Q8IUF8.1	Q8NFC6.1	P18577.1	Q5VSJ8.1

TABLE 7-continued

LIST OF ACCESSION NUMBERS FOR AUTOMIMMUNE ANTIGENS FROM IEDB

Q02161.1	P02663.1	P02769.1	Q9NWK9.1	O95415.1	Q7Z569.1	Q99728.1	Q9P287.1
Q9NRL2.1	Q9UIF9.1	Q58F21.1	P25440.1	Q15059.1	O60885.1	P18892.1	Q8NCU7.1
P04003.1	O75844.1	P12830.1	P33151.1	Q8NE86.1	P62158.1	P07384.1	P17655.1
P20810.1	P27797.1	O94985.1	P10644.1	P31321.1	P13861.1	O70739.1	Q8QVL3.1
Q8QVL6.1	Q8QVL9.1	Q91CY5.1	Q91CZ6.1	Q98Y63.1	Q99AQ9.1	Q9DTD4.1	Q9DUB7.1
Q9DUC1.1	Q9JG76.1	Q9QU30.1	Q9QUB8.1	Q80AR5.1	Q80QT8.1	Q8UZK7.1	P14348.1
Q9H2A9.1	P00918.1	P16870.1	O75339.1	O15519.1	Q14790.1	P04040.1	P35221.1
P49913.1	P07858.1	P07339.1	P25774.1	Q03135.1	Q16663.1	Q9H9A5.1	Q9Y5K6.1
P09326.1	P14209.1	Q99741.1	O00311.1	O75794.1	P04637.1	B2RD01.1	Q03188.1
P49454.1	Q9HC77.1	Q02224.1	P00450.1	P08622.1	P35514.1	Q05980.1	P9WMJ9.1
Q9H444.1	P36222.1	O00299.1	P05108.1	O15335.1	Q6UVK1.1	Q9P2D1.1	P10645.1
O75390.1	O14503.1	Q00610.1	P09497.1	O75508.1	P56750.1	Q9P2I0.1	Q7Z460.1
O75122.1	O75153.1	P10909.1	Q7Z401.1	P00451.1	P00488.1	P48444.1	P61923.1
E9PP50.1	P23528.1	Q8WUD4.1	Q49A88.1	Q16204.1	P38432.1	P02452.1	P02458.1
P05539.1	P02462.1	G1K238.1	Q7SIB2.1	P20908.1	Q02388.1	P27658.1	P12107.1
Q99715.1	Q05707.1	P39059.1	Q9UMD9.1	P08123.1	P08572.1	Q7SIB3.1	P05997.1
P12110.1	P13942.1	F1MZU6.1	Q01955.1	P12111.1	P02745.1	P02746.1	P09871.1
P01024.1	P0C0L5.1	P01031.1	Q07021.1	P13671.1	P02748.1	P08603.1	Q03591.1
Q6PUV4.1	W1Q7Z5.1	Q15021.1	Q15003.1	P42695.1	Q14746.1	Q9NZB2.1	Q12860.1
Q02246.1	P78357.1	Q9UBW8.1	P36717.1	P02741.1	P12277.1	P06732.1	H0Y8U5.1
Q13618.1	Q86VP6.1	P25024.1	P16220.1	P06493.1	P11802.1	Q00534.1	P50750.1
P41002.1	P04080.1	P50238.1	P52943.1	O14957.1	P20674.1	P10606.1	P14854.1
P15954.1	P10176.1	Q16678.1	P10635.1	Q14008.1	Q9Y5Y2.1	Q96KP4.1	P14416.1
Q5QP82.1	P07585.1	E5RFJ0.1	Q86SQ9.1	Q9Y394.1	P49366.1	Q5QJE6.1	P24855.1
Q02413.1	P32926.1	P15924.1	Q16760.1	P19572.1	A9NHS5.1	Q9JZ09.1	P06959.1
P08461.1	P10515.1	P20285.1	P0AFG6.1	Q5F875.1	P19262.1	P36957.1	Q16555.1
P53634.1	Q14689.1	Q13443.1	Q12959.1	Q15398.1	Q16531.1	P40692.1	P43246.1
P09884.1	P03198.1	P04293.1	Q9NRF9.1	Q9UGP5.1	P89471.1	Q13426.1	P49736.1
P33992.1	P11387.1	Q02880.1	Q9UBZ4.1	P24928.1	O14802.1	Q9NW08.1	P31689.1
P25686.1	O60216.1	O95793.1	P55265.1	Q6P0N6.1	Q13202.1	Q8IVF4.1	E9PEB9.1
Q9UII4.1	P11161.1	Q14258.1	Q9ULT8.1	O95714.1	Q7Z6Z7.1	Q9Y4L5.1	O43567.1
Q63HN8.1	Q969K3.1	Q8IUQ4.1	P19474.1	Q6AZZ1.1	Q9C026.1	Q14669.1	Q5T4S7.1
P18146.1	Q05BV3.1	Q6ZMW3.1	O95967.1	P15502.1	Q9BY07.1	P13804.1	Q6PJG2.1
A6PW80.1	P68104.1	P13639.1	Q96RP9.1	Q9BW60.1	Q9UI08.1	P17813.1	Q9NZ08.1
P14625.1	Q14511.1	Q6P2E9.1	B2RLL7.1	O84591.1	Q9Z7A6.1	P03188.1	P04578.1
P14075.1	Q6SW67.1	Q92817.1	P12724.1	Q12929.1	P61916.1	P07099.1	P03211.1
P12978.1	P12977.1	P03203.1	P03204.1	Q99808.1	P27105.1	P03372.1	P32519.1
Q15723.1	P60842.1	Q14240.1	P38919.1	P41567.1	Q14152.1	B5ME19.1	P60228.1
O75821.1	Q13347.1	Q9Y262.1	F1TIN3.1	Q96KP1.1	Q96A65.1	O84646.1	Q01780.1
P30822.1	O14980.1	P41180.1	P15311.1	Q08945.1	P52907.1	Q9BXW9.1	Q14296.1
Q16658.1	Q7L8L6.1	Q7L5A8.1	P49327.1	Q8IX29.1	Q8TB52.1	Q7Z6M2.1	Q7L513.1
Q9BZ67.1	A1ZL39.1	P02792.1	P35555.1	P02671.1	P02675.1	P02679.1	Q06828.1
P02751.1	Q4ZHG4.1	P20930.1	P21333.1	P30043.1	O75955.1	Q14254.1	P49771.1
Q12841.1	Q13461.1	P32314.1	O95954.1	P04075.1	P09972.1	P07954.1	Q9H0Q3.1
Q7Z6J4.1	P30279.1	P30281.1	O96020.1	O95067.1	P14078.1	P51570.1	Q08380.1
O00214.1	Q3B8N2.1	P34903.1	P09104.1	A4D1B5.1	P17900.1	P06396.1	Q12789.1
Q8WUA4.1	P03300.1	P08292.1	P27958.1	P03995.1	P14136.1	P47871.1	Q8TDQ7.1
P35575.1	Q9NQR9.1	Q9Z186.1	P11413.1	P06744.1	P48318.1	Q99259.1	P48320.1
Q05329.1	Q05683.1	P00367.1	Q05586.1	Q5VSF9.1	Q12879.1	S0G235.1	P15104.1
Q06210.1	P35754.1	P18283.1	P09211.1	P04406.1	Q9NPB8.1	P11216.1	P06737.1
P11217.1	Q31BS5.1	P04921.1	O43292.1	P30419.1	D6RB28.1	Q96S52.1	Q969N2.1
Q86SQ4.1	Q9HC97.1	K7EQ05.1	P28799.1	P0A6P5.1	P44536.1	Q8WWP7.1	P62826.1
P16520.1	P09471.1	Q9BVP2.1	Q9NVN8.1	P00738.1	Q9Y6N9.1	Q96CS2.1	P48723.1
Q0VDF9.1	P08107.1	P34931.1	P11142.1	P04792.1	P07900.1	Q14568.1	P08238.1
P54652.1	Q15477.1	P03452.1	P69905.1	P68871.1	P02042.1	P69892.1	P02790.1
Q14CZ8.1	P09651.1	Q32P51.1	P14866.1	Q8WVV9.1	O43390.1	Q1KMD3.1	O88569.1
P22626.1	Q9Y241.1	O95263.1	P12314.1	P09429.1	P26583.1	P25021.1	P49773.1
Q9NQE9.1	P12081.1	Q9NVP2.1	Q8WUI4.1	Q9H0E3.1	P07305.1	Q02539.1	P16403.1
P16402.1	P10412.1	P16401.1	P0CE15.1	Q92522.1	P0C0S8.1	P0C0S9.1	Q93077.1
Q9BTM1.1	Q71UI9.1	P0C0S5.1	P16104.1	P62808.1	P33778.1	P62807.1	P10853.1
P06899.1	O60814.1	Q99877.1	Q16778.1	Q5QNW6.1	P57053.1	P68431.1	P68432.1
Q16695.1	Q71DI3.1	P49450.1	P62803.1	P62805.1	P62806.1	Q99525.1	P02259.1
Q9NR48.1	P01892.1	P04439.1	P16188.1	P10314.1	P01891.1	P10316.1	P13747.1
P30464.1	P03989.1	P30685.1	P18463.1	Q95365.1	P30480.1	P30484.1	P30486.1
P18464.1	P30490.1	P30495.1	P01889.1	Q31612.1	P30460.1	Q07000.1	Q29960.1
F8W9Z8.1	Q29963.1	P10321.1	P28068.1	P20036.1	P04440.1	P01909.1	P01906.1
E9PIB1.1	P01920.1	Q5Y7D6.1	P01903.1	P79483.1	P13762.1	Q30154.1	P04229.1
P20039.1	Q95IE3.1	Q5Y7A7.1	P01911.1	Q29974.1	P01912.1	P13760.1	Q9GZN2.1
Q9H2X6.1	Q9H422.1	P51610.1	P50502.1	295441875.1	295413967.1	295413927.1	295413946.1
295441907.1	295441886.1	295413949.1	312192955.1	295413970.1	295413952.1	295413922.1	295413835.1
295413838.1	295413935.1	295413976.1	P01880.1	Q9Y6R7.1	Q9Y5U9.1	Q5VY09.1	O14498.1
P78318.1	O00410.1	P11314.1	Q9BY32.1	P01317.1	A6XGL2.1	P01308.1	F8WCM5.1
P01325.1	P01326.1	O15503.1	Q13429.1	P01344.1	Q9Y287.1	O60478.1	Q8N201.1
P23229.1	Q13349.1	P08514.1	P05106.1	P16144.1	Q9H0C8.1	Q14624.1	Q9UMF0.1
P01562.1	P01563.1	P01574.1	P38484.1	P14316.1	Q15306.1	Q13568.1	P20591.1

TABLE 7-continued

LIST OF ACCESSION NUMBERS FOR AUTOMIMMUNE ANTIGENS FROM IEDB

P20592.1	Q9BYX4.1	O14879.1	Q12905.1	Q12906.1	P42701.1	Q5TF58.1	Q9NZM3.1
P03956.1	Q9Y547.1	Q13099.1	O60306.1	O84606.1	Q9Y283.1	P10997.1	Q05084.1
Q9P266.1	Q53G59.1	P13645.1	P02533.1	P08779.1	Q04695.1	P05783.1	P35527.1
P04264.1	P35908.1	P12035.1	P48668.1	P08729.1	Q07666.1	Q96EK5.1	P52732.1
Q96Q89.1	Q99661.1	P01042.1	Q6NY19.1	Q13601.1	Q04760.1	P42166.1	P19137.1
P11047.1	O43813.1	P0CC04.1	P23700.1	P46379.1	Q6SW84.1	P13285.1	O75845.1
P40126.1	Q99538.1	P29536.1	P02750.1	Q15345.1	Q8NHL6.1	Q8NHJ6.1	Q6GTX8.1
Q9NPC1.1	Q14847.1	P61968.1	P11182.1	P18428.1	P50851.1	P06858.1	P0A5J0.1
P9WK61.1	Q86W92.1	P05451.1	P23141.1	P07195.1	P31994.1	P31995.1	P01130.1
Q7Z4F1.1	A4QPB2.1	P20132.1	P05455.1	P18627.1	Q13094.1	P01374.1	Q8NHM5.1
O60341.1	P10253.1	O00754.1	P10619.1	Q13571.1	P11279.1	Q9UQV4.1	P22897.1
P14174.1	P34810.1	Q8NDA8.1	P06491.1	P07199.1	F5HDQ6.1	P03227.1	Q14764.1
P08392.1	P40925.1	P40926.1	Q8N5Y2.1	Q9ULC4.1	Q96IJ6.1	H3BT46.1	P11226.1
Q8WXG6.1	Q92585.1	P43243.1	P50281.1	P51512.1	Q9NPA2.1	P03485.1	Q96RN5.1
A6ZJ87.1	Q99705.1	P40967.1	Q01726.1	Q16655.1	P15529.1	190341000.1	F5HB52.1
O00562.1	P16035.1	P56192.1	Q9UBB5.1	Q29983.1	Q16891.1	P55082.1	P55083.1
P46821.1	P27816.1	Q9UPY8.1	Q9Y2H9.1	Q504T8.1	Q8N183.1	P03107.1	P26539.1
P36745.1	P50799.1	Q81023.1	Q8TCT9.1	Q9H2D1.1	O60830.1	O94826.1	Q8IWA4.1
P28482.1	Q16584.1	O43318.1	O43683.1	Q9Y3D0.1	P08571.1	E7EWX8.1	Q99549.1
Q04360.1	Q96T58.1	Q8WXI7.1	Q9H8L6.1	P11229.1	P20309.1	Q5VZF2.1	O00499.1
P01106.1	P02687.1	P25188.1	P25274.1	P81558.1	F7A0B0.1	P02686.1	P02689.1
P25189.1	P60201.1	P60202.1	P20916.1	Q13875.1	E9PG44.1	Q16653.1	Q5SUK5.1
P24158.1	P41218.1	Q969H8.1	Q8WXC6.1	P05164.1	Q9NPC7.1	Q9H1R3.1	P35749.1
P35579.1	Q09013.1	O95248.1	O14745.1	O84639.1	P15586.1	P54450.1	Q8IXJ6.1
O95167.1	O95298.1	P19404.1	O75251.1	Q6N069.1	Q73WP1.1	Q86VF7.1	Q9BT67.1
O75113.1	Q15843.1	Q13564.1	Q8IXH7.1	P58400.1	P58401.1	Q09666.1	P12036.1
P07196.1	P07197.1	Q8NEJ9.1	Q13491.1	P59665.1	P08246.1	Q9Y6K9.1	Q9NV10.1
P43490.1	Q14112.1	Q5JPE7.1	P69849.1	O95897.1	Q13253.1	P05114.1	P05204.1
P80272.1	Q15233.1	P29597.1	P23497.1	P08651.1	Q14938.1	Q16236.1	P19838.1
Q6P4R8.1	O75694.1	P52948.1	P11654.1	Q8TEM1.1	Q9QY81.1	B4DW92.1	Q9Y6Q9.1
Q9H1E3.1	P67809.1	Q9H8H0.1	P78316.1	O00567.1	Q9Y2X3.1	Q9NR30.1	P19338.1
O75607.1	Q8NFH5.1	P03466.1	P0C025.1	Q99733.1	Q12830.1	Q96RS6.1	Q9H209.1
A6NMS3.1	P23515.1	Q9HD40.1	295413917.1	295413964.1	295441897.1	Q9PWU2.1	P0C675.1
P11926.1	P54368.1	P10451.1	A2T3P5.1	A2T3T2.1	Q8TAD7.1	Q9BXB4.1	Q9UBL9.1
P03262.1	Q96ST3.1	P50897.1	Q8IXS6.1	Q6ZV29.1	Q6ZW49.1	Q9UBV8.1	Q15154.1
O60664.1	Q01453.1	O60437.1	P32119.1	O43808.1	Q13794.1	Q9H2J4.1	Q8IZ21.1
Q92903.1	O95674.1	Q9UKL6.1	P04180.1	P30086.1	O00329.1	P42356.1	O14986.1
P57054.1	O95394.1	E4NG02.1	P00558.1	P18669.1	P15259.1	Q96FE7.1	Q9Y263.1
Q13393.1	P26276.1	Q2FZ93.1	B2RID6.1	Q9Y617.1	P05155.1	P00747.1	O25249.1
P13796.1	P07359.1	P16234.1	Q96CS7.1	Q9H7P9.1	Q15149.1	O43660.1	Q8IUK5.1
Q6UX71.1	P09874.1	Q460N5.1	Q9UKK3.1	Q15365.1	Q15366.1	Q9BY77.1	A6Q6E9.1
B2RGP7.1	295413956.1	I6XH73.1	Q96FM1.1	O43525.1	P19156.1	P18434.1	P0CG38.1
Q16633.1	O84616.1	O75915.1	O84647.1	P68950.1	P02545.1	Q6P2Q9.1	O43143.1
Q9HCS7.1	Q96IZ0.1	P9WQ27.1	O84288.1	Q92841.1	Q15751.1	Q7Z333.1	O84419.1
O84818.1	B2RJ72.1	Q8N0Y7.1	O60312.1	Q9UHA3.1	P89479.1	Q9H3G5.1	Q02809.1
P07737.1	Q8WUM4.1	Q53EL6.1	P49683.1	P12004.1	Q9UQ80.1	Q7Z6L0.1	Q07954.1
P13674.1	C9JIZ6.1	Q9H7Z7.1	P40306.1	P49720.1	P28074.1	O60678.1	O14744.1
P03189.1	P78543.1	O75629.1	O84583.1	O60888.1	P30101.1	Q14554.1	Q96JJ7.1
P03129.1	Q9H8V3.1	Q96PZ2.1	Q8WU58.1	Q96IP4.1	Q92636.1	Q96JP0.1	Q4ZG55.1
Q9ULI3.1	Q96ST2.1	Q7Z3U7.1	P33215.1	Q8NHV4.1	Q9UFN0.1	O60502.1	Q6UWS5.1
Q86U86.1	P23297.1	P60903.1	P06702.1	P04271.1	Q9UPN6.1	Q6PI26.1	Q6ZMD2.1
Q9BVV6.1	P14079.1	Q8WUY1.1	P50616.1	O15027.1	Q15436.1	Q15437.1	D4ACF2.1
Q9QJ57.1	Q9QJ42.1	Q70J99.1	Q9GZT5.1	B1AQ67.1	Q9UM07.1	P21980.1	Q92954.1
Q96JQ0.1	Q9JZQ0.1	A6NMY6.1	Q6FDV9.1	Q5VTE0.1	548558395.1	Q2VIR3.1	Q58FF8.1
Q9HCE1.1	P13985.1	A2RGE9.1	Q8IXJ9.1	Q6P2P2.1	D3HT40.1	P42588.1	56160925.1
Q53H96.1	P08559.1	H0YD97.1	O00330.1	P14618.1	Q9BXR0.1	Q9H974.1	Q9H2M9.1
P35241.1	Q14699.1	P0DJD1.1	Q9BYM8.1	A6NK89.1	P61106.1	B2RHG7.1	P04626.1
Q13546.1	Q92932.1	Q16849.1	P78509.1	P03209.1	P35249.1	P15927.1	P27694.1
O75678.1	Q14257.1	Q9NQC3.1	Q9BZR6.1	P10276.1	P10826.1	P49788.1	Q8TC12.1
P10745.1	P02753.1	P52566.1	Q7Z6I6.1	Q9BRR9.1	Q15052.1	Q8IY67.1	P11908.1
Q15418.1	Q9UK32.1	O43159.1	Q9ULK6.1	Q7L0R7.1	Q9C0B0.1	Q9H0A0.1	O00472.1
P18333.1	Q6PD62.1	Q9NTZ6.1	Q5T481.1	Q96EV2.1	Q9BQ04.1	P35637.1	Q9UKM9.1
P22087.1	Q9Y230.1	P31153.1	Q9NSC2.1	O94885.1	Q93084.1	P08168.1	P10523.1
Q9BQB4.1	O14828.1	Q13018.1	Q9UHJ6.1	Q9H4L4.1	Q9GZR1.1	Q15019.1	Q14141.1
O15270.1	Q92743.1	O43464.1	P49842.1	Q9BZL6.1	O15075.1	Q96GX5.1	Q8TD19.1
Q13153.1	F5GWT4.1	P63151.1	A6PVN5.1	Q06190.1	P53041.1	Q8N8A2.1	Q13315.1
P49591.1	Q86SQ7.1	P02787.1	P36952.1	Q14140.1	B7WNR0.1	P02768.1	Q9BYB0.1
Q5T123.1	Q9BZZ2.1	P67812.1	Q9BY50.1	P61009.1	P37108.1	P42224.1	Q92783.1
Q96FS4.1	Q9UIB8.1	O75094.1	Q55732.1	O00193.1	Q7Z3B0.1	P62304.1	P62306.1
P62308.1	P62314.1	P62316.1	P62318.1	P63162.1	P14678.1	P53814.1	Q13573.1
Q63008.1	P05023.1	Q96K37.1	Q9NQZ2.1	Q96L92.1	Q14515.1	Q13813.1	Q01082.1
P63208.1	P21453.1	P23246.1	M5JGM9.1	Q9NY15.1	Q7KZF4.1	Q9NQZ5.1	P16949.1
P05093.1	P08686.1	P36956.1	Q12772.1	Q7Z7C7.1	Q96BY9.1	P38646.1	P08254.1
Q14683.1	O95347.1	Q8IY18.1	P07566.1	P51649.1	P14410.1	O00391.1	O75897.1
Q8NDZ2.1	P00441.1	O14512.1	Q8IWZ8.1	Q6UWL2.1	Q8TAQ2.1	O15056.1	P60880.1

TABLE 7-continued

LIST OF ACCESSION NUMBERS FOR AUTOMIMMUNE ANTIGENS FROM IEDB

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

Predicting the Immunological Response of an Individual to a Polypeptide Antigen

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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, anaphlyaxis
Epoetin	Antibody-mediated pure red cell aplasia
Erythropoietin	pure red cell aplasia
Etanercept	no apparent effect on safety
Factor-IX	anaphylaxis
Infliximab	anaphylaxis

TABLE 8-continued

Example drugs associated with ADA-related adverse events

Drug	ADA-related adverse event
OKT3	anaphylaxis
Pegloticase	anti-dug antibody, treatment failure
rIFN-beta	anaphylaxis
recombinant factor VIII	anaphylaxis
Thrombopoietin	thrombocitopenia
Ustekinumab	anti-ustekinumab antibodies, affected treatment efficacy

[0129] 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).

[0130] 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.

[0131] 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 that one sequence that is a T cell epitope capable of binding to at least two, or in some cases at least three HLA class I molecules of the subject.

[0132] 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.

[0133] 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.

[0134] Without wishing to be bound by theory, one reason for the increased likelihood of deriving clinical benefit from a vaccine/immunotherapy comprising at least two multiple-HLA binding PEPIs, is that diseased cell populations, such as cancer or tumor cells or cells infected by viruses or pathogens such as HIV, are often heterogenous both within and between 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 PEPIs are included or targeted by a vaccine/immunotherapy because a patient is less likely to develop resistance to the composition through mutation of the target PEPI(s).

[0135] The likelihood that a subject will respond to treatment is therefore increased by (i) the presence of more multiple HLA-binding PEPIs in the active ingredient polypeptides; (ii) the presence of PEPIs in more target polypeptide antigens; and (iii) (over-)expression of the target polypeptide antigens in the subject or in diseased cells of the subject. In some cases expression of the target polypeptide

antigens in the subject may be known, for example if target polypeptide antigens are in a sample obtained from the subject. In other cases, the probability that a specific subject, or diseased cells of a specific subject, (over-)express a specific or any combination of target polypeptide antigens may be determined using population expression frequency data. The population expression frequency data may relate to a subject- and/or disease-matched population or the intent-to-treat population. For example, the frequency or probability of expression of a particular cancer-associated antigen in a particular cancer or subject having a particular cancer, for example breast cancer, can be determined by detecting the antigen in tumor, e.g. breast cancer tumor samples. In some cases such expression frequencies may be determined from published figures and scientific publications. In some cases a method of the invention comprises a step of determining the expression frequency of a relevant target polypeptide antigen in a relevant population.

[0136] 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.

[0137] 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 e 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.

[0138] PEPI3+ count—immunogenicity of a vaccine in a subject: Vaccine-derived PEPI3+ are personal epitopes that bind to et least 3 HLAs of a subject and induce T cell responses. PEPI3+ can be determined using the PEPI3+ Test in subjects who's complete 4-digit HLA genotype is known.

[0139] 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).

[0140] 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.

[0141] 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).

[0142] AGP50—effectiveness of a cancer vaccine in a population: The mean number of vaccine antigens expressed in the indicated tumor with PEPI (i.e., AGP) in a population. The AGP50 indicates the mean number of tumor antigens that the T cell responses induced by the vaccine can recognize. AGP50 is dependent on the expression rate of the antigens in the indicated tumor type and the immunogenicity of the antigens in the target population. AGP50 can estimate a vaccine's effectiveness in different populations and can be used to compare different vaccines in the same population. The computation of AGP50 is similar to that used for AG50, except the expression is weighted by the occurrence of the PEPI3+ in the subject on the expressed vaccine antigens. In a theoretical population, where each subject has a PEPI from each vaccine antigen, the AGP50 will be equal to AG50. In another theoretical population, where no subject has a PEPI from any vaccine antigen, the AGP50 will be 0. In general, the following statement is valid: $0 \leq AGP50 \leq AG50$.

[0143] mAGP—a candidate biomarker for the selection of likely responders: Likelihood that a cancer vaccine induces T cell responses against multiple antigens expressed in the indicated tumor. mAGP is calculated from the expression rates of vaccine-antigens in e.g. the tumor and the presence of vaccine derived PEPIs in the subject. Technically, based on the AGP distribution, the mAGP is the sum of probabilities of the multiple AGP (≥ 2 AGPs).

[0144] 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 PEPI3+ count (for example 2, 3, 4, 5,

6, 7, 8, 9, 10, 11, or 12 or more PEPI3+), 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

[0145] 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.

[0146] 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.

[0147] The method may comprise determining whether the polypeptide(s) comprises a sequence that is a T cell epitope capable of binding to at least two, or in other cases to at least three HLA class I molecules of the subject. In some cases the method comprises determining that the polypeptide comprises a sequence that is a T cell epitope capable of binding to at least four, or at least five HLA class I molecules of the subject; or an amino acid sequence that is a T cell epitope capable of binding to at least four, or at least five, or at least six or at least seven HLA class II of the subject. The method may further comprise identifying said sequence as toxic immunogenic for the subject or predicting a toxic immune response in the subject. In other cases no such amino acid sequence is identified and the method further comprises predicting no toxic immune response in the subject. The method may further comprise selecting or recommending for treatment of the subject administration of one or more polypeptides or a pharmaceutical composition that is predicted to induce no or low immune-toxicity, and optionally further treating the subject by administering the polypeptide. The disclosure also provides a method of treating a subject in need thereof by administrating to the subject such a polypeptide or composition.

[0148] 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 PEPIs in the polypeptide or to reduce the number of HLA class I or class II molecules of the subject or of said population that bind to the fragment of the polypeptide that is identified as immunogenic in the subject or in a proportion of said population. In some cases the mutation may reduce or prevent a toxic immune response or may increase the efficacy by preventing the ADA development in the subject or in a proportion of said population. The mutated polypeptide may be further selected or recommended for treatment of the subject or of a subject of said population. The subject may further be treated by administration of the mutated polypeptide. The disclosure also provides a method of treating a subject in need thereof by administrating to the subject such a mutated polypeptide.

Predicting the Response of an Individual to Treatment with a Checkpoint Inhibitor

[0149] 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.

[0150] 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 popu-

lation. 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.

[0151] 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.

[0152] 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.

[0153] 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 subject has been predicted to respond to administration of a checkpoint inhibitor by the method described herein.

[0154] 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 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

[0155] 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 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.

[0156] 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, treat, or cure a disease of an individual, such as a cancer.

[0157] 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 with the same disease or condition, pathogenic organism or group of pathogenic organisms or virus, or type of cancer.

[0158] 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 herein, which consecutive amino acids comprise the amino acid sequence of the PEPI.

[0159] In some cases the amino acid sequence is flanked at the N and/or C terminus by additional amino acids that are not part of the consecutive sequence of the target polypeptide antigen. In some cases the sequence is flanked by up to 41 or 35 or 30 or 25 or 20 or 15 or 10, or 9 or 8 or 7 or 6 or 5 or 4 or 3 or 2 or 1 additional amino acid at the N and/or C terminus or between target polypeptide fragments. In other cases each polypeptide either consists of a fragment of a target polypeptide antigen, or consists of two or more such fragments arranged end to end (arranged sequentially in the peptide end to end) or overlapping in a single peptide (where two or more of the fragments comprise partially overlapping sequences, for example where two PEPIs in the same polypeptide are within 50 amino acids of each other).

[0160] 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/).

[0161] The at least two multiple HLA-binding PEPIs of the composition polypeptides may both target a single antigen (e.g a polypeptide vaccine comprising two multiple HLA-binding PEPIs derived from a single antigen, for example a tumor associated antigen, targeted by the vaccine/immunotherapy) or may target different antigens (e.g. a polypeptide vaccine comprising one multiple HLA-binding PEPI derived from one antigen, e.g. a tumor associated antigen, and a second multiple HLA-binding PEPI derived from a different antigen, e.g. a different tumor associated antigen, both targeted by the vaccine/immunotherapy).

[0162] 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 PEPIs. The PEPIs 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.

[0163] Currently most vaccines and immunotherapy compositions target only a single polypeptide antigen. However according to the present disclosure it is in some cases beneficial to provide a pharmaceutical composition or an active ingredient polypeptide that targets two or more different polypeptide antigens. For example, most cancers or tumors are heterogeneous, meaning that different cancer or tumor cells of a subject (over-)express different antigens. The tumour cells of different cancer patients also express different combinations of tumour-associated antigens. The anti-cancer immunogenic compositions that are most likely to be effective are those that target multiple antigens expressed by the tumor, and therefore more cancer or tumor cells, in an individual human subject or in a population.

[0164] The beneficial effect of combining multiple PEPIs in a single treatment (administration of one or more pharmaceutical compositions that together comprise multiple PEPIs), can be illustrated by the personalised vaccine polypeptides described in Examples 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 PEPIs in only BAGE and MAGE A9, then the probability of having a mAGP (multiple expressed antigens with PEPI) would be 11%. If patent XYZ were treated with a vaccine comprising only PEPIs for the MAGE A4 and MAGE A10 CTAs, then the probability of having a multiAGP would be 19%. However if a vaccine contained all 4 of these CTAs (BAGE, MAGE A9, MAGE A4 and MAGE A10), then the probability of having a mAGP would be 50%. In other words the effect would be greater than the combined probabilities of mAGP for both two-PEPI treatments (probability mAGP for BAGE/MAGE+ probability mAGP for MAGE A4 and MAGE A10). Patient XYZ's PIT vaccine described in Example 17 contains a further 9 PEPIs, and thus, the probability of having a mAGP is over 99.95%.

[0165] 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%.

[0166] 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.

[0167] 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.

[0168] In other cases one or more or each of the immunogenic polypeptide fragments is from a target polypeptide antigen that is not generally expressed or is minimally expressed in normal healthy cells or tissue, but is expressed in a high proportion of (with a high frequency in) subjects or in the diseased cells of a subject having a particular disease or condition, as described above. The method my comprise identifying or selecting such a target polypeptide antigen. In some cases two or more or each of the immunogenic polypeptide fragments/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 frag-

ments 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.

[0169] 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.

[0170] 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

[0171] 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.

[0172] 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.

[0173] 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).

[0174] 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.

[0175] 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.

[0176] 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).

[0177] 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%.

[0178] 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).

[0179] 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.

[0180] In order to increase the immunogenicity of the composition, the pharmacological compositions may comprise one or more adjuvants and/or cytokines.

[0181] 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, bio adhesives 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.

[0182] In some embodiments, the compositions comprise an adjuvant selected from the group consisting of Montanide ISA-51 (Seppic, Inc., Fairfield, N.J., United States of America), QS-21 (Aquila Biopharmaceuticals, Inc., Lexington, Mass., United States of America), GM-CSF, cyclophosamide, bacillus Calmette-Guerin (BCG), corynbacterium parvum, levamisole, azimezone, isoprinisone, dinitrochlorobenezene (DNCB), keyhole limpet hemocyanins (KLH), Freunds adjuvant (complete and incomplete), mineral gels, aluminum hydroxide (Alum), lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, diphtheria toxin (DT).

[0183] 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 (I1) such as but not limited to IL-1, IL-1.alpha., IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; IL-13, IL-14, IL-15, IL-16, IL-17, IL-18; LIF; kit-ligand or FLT-3; angiostatin; thrombospondin; endostatin; a tumor necrosis factor (TNF); and LT.

[0184] 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%.

[0185] In certain aspects, the pharmaceutical compositions of the disclosure are prepared by physically mixing the adjuvant and/or cytokine with the PEPIs under appropriate sterile conditions in accordance with known techniques to produce the final product.

[0186] 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, U.S. Pat. No. 4,235,877.

[0187] 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.

[0188] 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.

[0189] Polynucleotide or oligonucleotide components may be naked nucleotide sequences, or be in combination with cationic lipids, polymers or targeting systems. They may be delivered by any available technique. For example, the polynucleotide or oligonucleotide may be introduced by needle injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the polynucleotide or oligonucleotide may be delivered directly across the skin using a delivery device such as particle-mediated gene delivery. The polynucleotide or oligonucleotide may be administered topically to the skin, or to mucosal surfaces for example by intranasal, oral, or intrarectal administration.

[0190] Uptake of polynucleotide or oligonucleotide constructs may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example, calcium phosphate and DEAE-Dextran and lipofectants, for example, lipofectam and transfectam. The dosage of the polynucleotide or oligonucleotide to be administered can be altered.

[0191] Administration is typically in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be, although prophylaxis may be considered therapy), this being sufficient to result in a clinical response or to show clinical benefit to the individual, e.g. an effective amount to prevent or delay onset of the disease or condition, to ameliorate one or more symptoms, to induce or prolong remission, or to delay relapse or recurrence.

[0192] The dose may be determined according to various parameters, especially according to the substance used; the age, weight and condition of the individual to be treated; the route of administration; and the required regimen. The amount of antigen in each dose is selected as an amount which induces an immune response. A physician will be able to determine the required route of administration and dosage for any particular individual. The dose may be provided as a single dose or may be provided as multiple doses, for example taken at regular intervals, for example 2, 3 or 4 doses administered hourly. Typically peptides, polynucleotides or oligonucleotides are typically administered in the range of 1 pg to 1 mg, more typically 1 pg to 10 μg for particle mediated delivery and 1 μg to 1 mg, more typically 1-100 μg, more typically 5-50 μg for other routes. Generally, it is expected that each dose will comprise 0.01-3 mg of antigen. An optimal amount for a particular vaccine can be ascertained by studies involving observation of immune responses in subjects.

[0193] Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

[0194] In some cases in accordance with the disclosure, more than one peptide or composition of peptides is administered. Two or more pharmaceutical compositions may be administered together/simultaneously and/or at different times or sequentially. Thus, the disclosure includes sets of pharmaceutical compositions and uses thereof. The use of combination of different peptides, optionally targeting different antigens, is important to overcome the challenges of genetic heterogeneity of tumors and HLA heterogeneity of individuals. Multiple pharmaceutical compositions of PEPIs, manufactured for use in one regimen, may define a drug product.

[0195] 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.

[0196] The skilled artisan will recognize that compositions of the disclosure may also be administered in one, or more doses, as well as, by other routes of administration. For example, such other routes include, intracutaneously, intravenously, intravascularly, intraarterially, intraperitnoeally, intrathecally, intratracheally, intracardially, intralobally, intramedullarly, intrapulmonarily, and intravaginally. Depending on the desired duration of the treatment, the compositions according to the disclosure may be administered once or several times, also intermittently, for instance on a monthly basis for several months or years and in different dosages.

[0197] Solid dosage forms for oral administration include capsules, tablets, caplets, pills, powders, pellets, and granules. In such solid dosage forms, the active ingredient is ordinarily combined with one or more pharmaceutically acceptable excipients, examples of which are detailed above. Oral preparations may also be administered as aqueous suspensions, elixirs, or syrups. For these, the active ingredient may be combined with various sweetening or flavoring agents, coloring agents, and, if so desired, emulsifying and/or suspending agents, as well as diluents such as water, ethanol, glycerin, and combinations thereof.

[0198] 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.

[0199] In some cases the treatment may be administered in combination with checkpoint blockade therapy/checkpopint inhibitors, co-stimulatory antibodies, cytotoxic or non-cytotoxic chemotherapy and/or radiotherapy, targeted therapy or monoclonal antibody therapy. It has been demonstrated that chemotherapy sensitizes tumors to be killed by tumor specific cytotoxic T cells induced by vaccination (Ramakrishnan et al. *J Clin Invest.* 2010; 120(4):1111-1124). Examples of chemotherapy agents include alkylating agents including nitrogen mustards such as mechlorethamine (HN2), cyclophosphamide, ifosfamide, melphalan (L-sarcolysin) and chlorambucil; anthracyclines; epothilones; nitrosoureas such as carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU) and streptozocin (streptozotocin); triazenes such as decarbazine (DTIC; dimethyltriazenoimidazole-carboxamide; ethylenimines/methylmelamines such as hexamethylmelamine, thiotepa; alkyl sulfonates such as busulfan; Antimetabolites including folic acid analogues such as methotrexate (amethopterin); alkylating agents, antimetabolites, pyrimidine analogs such as fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorodeoxyuridine; FUdR) and cytarabine (cytosine arabinoside); purine analogues and related inhibitors such as mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG) and pentostatin (2'-deoxycoformycin); epipodophylotoxins; enzymes such as L-asparaginase; biological response modifiers such as IFNα, IL-2, G-CSF and GM-CSF; platinum coordination complexes such as cisplatin (cis-DDP), oxaliplatin and carboplatin; anthracenediones such as mitoxantrone and anthracycline; substituted urea such as hydroxyurea; methylhydrazine derivatives including procarbazine (N-methylhydrazine, MIH) and procarbazine; adrenocortical suppressants such as mitotane (o,p'-DDD) and aminoglutethimide; taxol and analogues/derivatives; hormones/hormonal therapy and agonists/antagonists including adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide, progestin such as hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate, estrogen such as diethylstilbestrol and ethinyl estradiol equivalents, antiestrogen such as tamoxifen, androgens including testosterone propionate and fluoxymesterone/equivalents, antiandrogens such as flutamide, gonadotropin-releasing hormone analogs and leuprolide and non-steroidal antiandrogens such as flutamide; natural products including vinca alkaloids such as vinblastine (VLB) and vincristine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin) and mitomycin (mitomycin C), enzymes such as L-asparaginase, and biological response modifiers such as interferon alphenomes.

[0200] In some cases the method of treatment is a method of vaccination or a method of providing immunotherapy. As used herein, "immunotherapy" is the treatment of a disease or condition by inducing or enhancing an immune response in an individual. In certain embodiments, immunotherapy refers to a therapy that comprises the administration of one or more drugs to an individual to elicit T cell responses. In a specific embodiment, immunotherapy refers to a therapy that comprises the administration or expression of polypeptides that contain one or more PEPIs to an individual to elicit a T cell response to recognize and kill cells that display the one or more PEPIs on their cell surface in conjunction with a class I HLA. In another specific embodiment, immunotherapy comprises the administration of one or more PEPIs to an individual to elicit a cytotoxic T cell response against cells that display tumor associated antigens (TAAs) or cancer testis antigens (CTAs) comprising the one or more PEPIs on their cell surface. In another embodiment, immunotherapy refers to a therapy that comprises the administration or expression of polypeptides that contain one or more PEPIs presented by class II HLAs to an individual to elicit a T helper response to provide co-stimulation to cytotoxic T cells that recognize and kill diseased cells that display the one or more PEPIs on their cell surface in conjunction with

a class I HLAs. In still another specific embodiment, immunotherapy refers to a therapy that comprises administration of one or more drugs to an individual that re-activate existing T cells to kill target cells. The theory is that the cytotoxic T cell response will eliminate the cells displaying the one or more PEPIs, thereby improving the clinical condition of the individual. In some instances, immunotherapy may be used to treat tumors. In other instances, immunotherapy may be used to treat intracellular pathogen-based diseases or disorders.

[0201] 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).

[0202] 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

[0203] The disclosure provides a system comprising 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 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 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 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 pharmodynamic biomarker described herein.

Further Embodiments of the Disclosure

[0204] 1. A method of predicting whether a polypeptide or a fragment of a polypeptide is immunogenic for a specific human subject, the method comprising the steps of

[0205] (i) determining whether the polypeptide comprises:

[0206] (a) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0207] (b) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

[0208] (ii) predicting

[0209] 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

[0210] 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)

[0211] 2. A method of identifying a fragment of a polypeptide as immunogenic for a specific human subject, the method comprising the steps of

[0212] (i) determining that the polypeptide comprises:

[0213] (a) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0214] (b) an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class II molecules of the subject; and

[0215] (ii) identifying said sequence as a fragment of the polypeptide that is immunogenic for the subject.

[0216] 3. The method of item 1 or item 2, wherein the T cell epitope is capable of binding to at least two 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 two HLA class II molecules of the subject and consists of 15 consecutive amino acids of the polypeptide.

[0217] 4. The method of any one of the preceding items, wherein step (i) comprises determining that the polypeptide comprises an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

[0218] 5. The method of any one of the preceding items, wherein 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.

[0219] 6. The method of any one of items 1 to 3, wherein 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.

[0220] 7. The method of item 4 or item 5 further comprising 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.

[0221] 8. The method of any one of the preceding items, wherein the polypeptide 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.

[0222] 9. The method of any one of the preceding items, wherein the polypeptide is selected from the antigens listed in Tables 2 to 6.

[0223] 10. The method of any one of the preceding items, wherein the polypeptide 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.

[0224] 11. The method of any one of the preceding items, wherein the polypeptide is a mutational neoantigen, optionally wherein

[0225] (a) the neoantigen is present in a sample obtained from the subject; and/or

[0226] (b) the immunogenic fragment comprises a neoantigen specific mutation.

[0227] 12. The method of any one of items 1 to 11, wherein all of the fragments of the polypeptide that are a T cell epitope capable of binding to at least two 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 two 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.

[0228] 13. The method of any one of the preceding items, 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

[0229] 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;

[0230] 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;

[0231] 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

[0232] 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.

[0233] 14. The method of item 13, wherein the subject is predicted to have a cytotoxic T cell and/or a helper T cell response, and 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

[0234] (i) identifying one or more polypeptide antigens that comprises an amino acid sequence that is

[0235] (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

[0236] (b) comprised in the amino acid sequence of the polypeptide(s)

[0237] (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.

[0238] 15. The method of item 13 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.

[0239] 16. The method of item 15, wherein the polypeptide is a checkpoint inhibitor.

[0240] 17. The method of any one of items 1 to 14 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

[0241] 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

[0242] 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.

[0243] 18. The method of item 17, 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).

[0244] 19. The method of any one of items 1 to 14, 17 and 18, 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:

[0245] (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;

[0246] (b) a higher number of target polypeptide antigens, comprising at least one amino acid sequence that is both

[0247] A. comprised in an active ingredient polypeptide; and

[0248] 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;

[0249] (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

[0250] A. comprised in an active ingredient polypeptide; and

[0251] B. a T cell epitope capable of binding to at least three HLA class I of the subject; and/or

[0252] (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

[0253] A. comprised in an active ingredient polypeptide; and

[0254] B. a T cell epitope capable of binding to at least three HLA class I of the subject.

[0255] 20. The method of any one of items 1 to 14, and 17 to 19, 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

[0256] (i) identifying which polypeptide antigens targeted by the active ingredient polypeptide(s) comprise an amino acid sequence that is both

[0257] A. comprised in an active ingredient polypeptide; and

[0258] B. a T cell epitope capable of binding to at least three HLA class I of the subject;

[0259] (ii) using population expression data for each antigen identified in step (i) to determine the probability that the subject expresses one or more of the antigens identified in step (i) that together comprise at least two different amino acid sequences of step (i); and

[0260] (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.

[0261] 21. The method of item 20, wherein step (ii) comprises 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).

[0262] 22. The method of item 21, 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).

[0263] 23. The method of any one of items 19 to 22, wherein one or more of the following factors

[0264] further correspond to a higher likelihood of a clinical response:

[0265] (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;

[0266] (b) a higher number of target polypeptide antigens comprising at least one amino acid sequence that is both

[0267] A. comprised in an active ingredient polypeptide; and

[0268] 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;

[0269] (c) a higher number of target polypeptide antigens comprising

[0270] i. at least one amino acid sequence that is both

[0271] A. comprised in an active ingredient polypeptide; and

[0272] B. a T cell epitope capable of binding to at least three HLA class I of the subject; and

[0273] ii. at least one amino acid sequence that is both

[0274] A. comprised in an active ingredient polypeptide; and

[0275] B. a T cell epitope capable of binding to at least three HLA class II of the subject;

[0276] (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

[0277] A. comprised in an active ingredient polypeptide; and

[0278] B. a T cell epitope capable of binding to at least three HLA class II of the subject

[0279] (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

[0280] i. at least one amino acid sequence that is both

[0281] A. comprised in an active ingredient polypeptide; and

[0282] B. a T cell epitope capable of binding to at least three HLA class I of the subject; and

[0283] ii. at least one amino acid sequence that is both

[0284] A. comprised in an active ingredient polypeptide; and

[0285] B. a T cell epitope capable of binding to at least three HLA class II of the subject;

[0286] (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

[0287] A. comprised in an active ingredient polypeptide; and

[0288] B. a T cell epitope capable of binding to at least three HLA class II of the subject;

[0289] and/or

[0290] (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

[0291] i. at least one amino acid sequence that is both

[0292] A. comprised in an active ingredient polypeptide; and

[0293] B. a T cell epitope capable of binding to at least three HLA class I of the subject; and

[0294] ii. at least one amino acid sequence that is both

[0295] A. comprised in an active ingredient polypeptide; and

[0296] B. a T cell epitope capable of binding to at least three HLA class II of the subject.

[0297] 24. The method of any one of items 19 to 23, 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.

[0298] 25. The method of any one of items 1 to 24, 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

[0299] (a) the polypeptide(s) comprises at least one amino acid sequence that

[0300] i. is capable of binding to at least three HLA class I of the subject; and

[0301] ii. corresponds to a fragment of a human polypeptide expressed in healthy cells;

[0302] and a toxic immune response is predicted; or

[0303] (b) the polypeptide(s) do not comprise any amino acid sequence that

[0304] A. is capable of binding to at least three HLA class I of the subject; and

[0305] B. corresponds to a fragment of a human polypeptide expressed in healthy cells;

[0306] and no toxic immune response is predicted.

[0307] 26. The method of any one of the preceding items 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.

[0308] 27. The method of item 26, further comprising administering one or more of the selected or recommended polypeptides or pharmaceutical compositions or the polypeptides of one or more kits or panels of polypeptides to the subject.

[0309] 28. A method of treatment of a human subject in need thereof, the method comprising administering to the subject a polypeptide that comprises a polypeptide fragment that has been identified as immunogenic, or a polypeptide that has been predicted to be immunogenic, or a polypeptide or pharmaceutical composition that has been predicted to induce a cytotoxic T cell or helper T cell response, or a pharmaceutical composition, kit or panel of polypeptides that has been predicted to induce a clinical response, or a pharmaceutical composition, kit or panel of polypeptides that has been determined to have a threshold minimum likelihood of inducing a clinical response, or a polypeptide or pharmaceutical composition that is predicted not to induce a toxic immune response or ADA development in the subject using a method according to any one of items 1 to 23, or one or more polypeptides or pharmaceutical compositions that have been selected or recommended for treatment of the subject using a method according to item 26.

[0310] 29. The method of any one of items 1 to 11, wherein the polypeptide is associated with or suspected of being associated with an autoimmune disorder or an autoimmune response in the subject and 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.

[0311] 30. The method of any one of items 1 to 12 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

[0312] 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

[0313] 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.

[0314] 31. The method of any one of items 1 to 12, further comprising determining the likelihood that the subject will have a clinical response to administration of a checkpoint inhibitor to treat cancer, the method comprising

[0315] (i) selecting a plurality of polypeptide antigens that are associated with the cancer type of the subject;

[0316] (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

[0317] (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.

[0318] 32. The method of item 30 or item 31 further comprising selecting or recommending administration of a checkpoint inhibitor for treatment of the subject.

[0319] 33. The method of item 32 further comprising administering a checkpoint inhibitor to the subject.

[0320] 34. A method of treatment of a human subject in need thereof, the method comprising administering to the subject a checkpoint inhibitor, wherein the subject has been predicted to respond, or to be likely to respond, to administration of a checkpoint inhibitor by a method according to item 30 or item 31.

[0321] 35. The method of any one of items 13, 15 to 18 and 30, 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.

[0322] 36. A method 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 method comprising:

[0323] (i) selecting a fragment of a polypeptide, which fragment has been identified as immunogenic for the subject by the method of any one of items 2 to 11;

[0324] (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

[0325] a. comprises the fragment selected in step (i); and

[0326] b. is a T cell epitope capable of binding at least three or to the most possible HLA class II molecules of the subject;

[0327] (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);

[0328] (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;

[0329] (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

[0330] (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.

[0331] 37. 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 arranged end to end or overlapping in a single peptide.

[0332] 38. The method of item 37, 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

[0333] (i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

[0334] (ii) is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0335] (iii) meets both requirements (i) and (ii).

[0336] 39. The method of any of items 36 to 38, wherein the one or more polypeptides have been screened to eliminate polypeptides comprising an amino acid sequence that

[0337] (i) corresponds to a fragment of a human polypeptide expressed in healthy cells; or

[0338] (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.

[0339] 40. A human subject-specific pharmaceutical composition, kit or panel of polypeptides for use in a method of inducing an immune response in a specific human subject, and designed or prepared for the subject according to the method of any one of items 36 to 39, wherein the composition or kit optionally comprises at least one pharmaceutically acceptable diluent, carrier, or preservative.

[0340] 41. 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 of 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.

[0341] 42. 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.

[0342] 43. The human subject-specific pharmaceutical composition, kit or panel of item 41 or item 42, wherein one or more or each of the peptides or regions comprises an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

[0343] 44. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 43, wherein one or more or each of the peptides or regions 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.

[0344] 45. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 44, wherein one or more or each of the peptides or regions 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.

[0345] 46. The human subject-specific pharmaceutical composition, kit or panel of item 44 or item 45 wherein one or more or each of the peptides or regions comprises an amino acid sequence that is a T cell epitope capable of binding at least one HLA class II molecule of the subject, wherein the HLA class II-binding T cell epitope comprises an amino acid sequence that is a T cell epitope capable of binding to at least two HLA class I molecules of the subject.

[0346] 47. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 46, wherein one or more or each of the peptides or regions comprises a sequence of up to 50 consecutive amino acids of a polypeptide that is expressed by a pathogenic organism, a virus or a cancer cell, is associated with an autoimmune

disorder, or is an allergen, wherein the sequence comprises the T cell epitope of the peptide or region that is capable of binding to at least two HLA class I or class II molecules of the subject, optionally wherein one or more or each of the polypeptide sequences is flanked at the N and/or C terminus by additional amino acids that are not part of the amino acid sequence of the polypeptide(s).

[0347] 48. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 47, wherein one or more of the polypeptide(s) are selected from the antigens listed in Tables 2 to 6.

[0348] 49. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 48, wherein the polypeptide(s) are antigens or neoantigens expressed by a cancer cell, optionally wherein the cancer cell is in a sample taken from the subject.

[0349] 50. The human subject-specific pharmaceutical composition, kit or panel of any one of items 41 to 49, wherein the polypeptide(s) are mutational neoantigen(s), optionally wherein the neoantigen(s) are present in a sample obtained from the subject; and/or the T cell epitope(s) each comprise a neoantigen specific mutation.

[0350] 51. The human subject-specific pharmaceutical composition, kit or panel of any one of items 47 to 50 wherein two or more or each of the polypeptide sequences of up to 50 consecutive amino acids are from different polypeptides.

[0351] 52. The human subject-specific pharmaceutical composition, kit or panel of any one of items 47 to 51, wherein one or more or each of the sequences of up to 50 consecutive amino acids comprises an amino acid sequence that

[0352] (a) 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

[0353] (b) is a T cell epitope capable of binding to at least three HLA class II molecules of the subject or to the most possible HLA class II molecules of the subject for a sequence comprising the HLA class I-binding epitope of (a).

[0354] 53. The human subject-specific pharmaceutical composition, kit or panel of item 47 to 52 wherein one or more or each polypeptide either

[0355] (a) consists of one of said sequence of up to 50 consecutive amino acids from a polypeptide that is expressed by a pathogenic organism, a virus or a cancer cell, is associated with an autoimmune disorder or is an allergen; or

[0356] (b) comprises or consist of two or more of said sequences of up to 50 consecutive amino acids arranged end to end or overlapping in a single peptide.

[0357] 54. The human subject-specific pharmaceutical composition, kit or panel of item 53 wherein the one or more peptides 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

[0358] (i) corresponds to a fragment of a human polypeptide expressed in healthy cells;

[0359] (ii) is a T cell epitope capable of binding to at least two HLA class I molecules of the subject; or

[0360] (iii) meets both requirements (i) and (ii).

[0361] 55. The human subject-specific pharmaceutical composition, kit or panel of any of items 41 to 54 wherein the one or more polypeptides do not comprise any amino acid sequences that

[0362] (i) corresponds to a fragment of a human polypeptide expressed in healthy cells; or

[0363] (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.

[0364] 56. A method of treatment comprising administering to a human subject in need thereof a human subject-specific pharmaceutical composition or the polypeptides of a kit or panel of polypeptides according to any one of items 41 to 55, wherein the pharmaceutical composition, kit or panel is specific for the subject, optionally wherein the method is for the treatment of cancer.

[0365] 57. The method of treatment according to any one of items 28, 34 and 56 wherein the treatment is administered in combination with chemotherapy, targeted therapy or a checkpoint inhibitor.

[0366] 58. 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.

[0367] 59. The method of item 58, which is

[0368] (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

[0369] (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.

[0370] 60. The method of item 58 or claim **59** further comprising administering the polypeptide to the subject.

[0371] 61. A method of inducing an immune response in a subject, the method comprising administering to the subject a polypeptide designed according to the method of item 58 or item 59.

[0372] 62. A method of inducing an immune response in a specific human subject, the method comprising designing or preparing a peptide according to the method of item 58 or item 59, and administering the peptide to the subject.

[0373] 63. A system comprising

[0374] (c) 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

[0375] (d) 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.

[0376] 64. The storage system of item 63 further comprising

[0377] (c) an output module configured to display

[0378] (i) a prediction of whether the one or more polypeptides is immunogenic for the subject; or the sequence of one or more fragments of the one or more polypeptides that are predicted to be immunogenic for the subject;

[0379] (ii) a prediction of whether the individual will have an immune response to administration of the one or more polypeptides or one or more pharmaceutical compositions comprising the one or more polypeptides as active ingredients;

[0380] (iii) a prediction of whether the subject will have a clinical response to a method of treatment comprising administering to the subject one or more pharmaceutical compositions comprising the one or more polypeptides as active ingredients;

[0381] (iv) the likelihood that the subject will have a clinical response to administration of one or more pharmaceutical compositions comprising the one or more polypeptides as active ingredients;

[0382] (v) a prediction of whether administration of the one or more polypeptides or one or more pharmaceutical compositions comprising the one or more polypeptides will induce a toxic immune response in the subject;

[0383] (vi) a prediction that the one or more polypeptides is associated with an autoimmune disorder in the subject;

[0384] (vii) a prediction of whether the subject will have a clinical response to administration of a checkpoint inhibitor;

[0385] (viii) a recommendation of whether or not the subject should be treated by administration of the one or more polypeptides and/or one or more pharmaceutical compositions.

Examples

Example 1—HLA-Epitope Binding Prediction Process and Validation

[0386] Predicted binding between particular HLA and epitopes (9 mer peptides) was based on the Immune Epitope Database tool for epitope prediction (www.iedb.org).

[0387] 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.

[0388] The rate of agreement with the experimentally determined dataset (Table 9) was determined. The binding HLA I-epitope pairs of the dataset were correctly predicted with a 93% probability. Coincidentally the non-binding HLA I-epitope pairs were also correctly predicted with a 93% probability.

TABLE 9

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

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

[0389] 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	Predicted number of HLAs binding to an epitope						
HLA binding	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%

[0390] 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

[0391] 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.

[0392] 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.

[0393] 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.

[0395] 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).

TABLE 11

Summary of patient datasets

Clinical trial	Immunotherapy	Target Antigen	Disease	# Patients*	# Data sets (#antigen × #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 × 17	IFN-γ ELISPOT	High Resolution SBT	1
2	HIVIS vaccine	HIV-1 Gag HIV-1 RT	AIDS	9/12	2 × 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 × 18	In vitro and Ex vivo IFN-γ ELISPOT	High Resolution SBT	3 4
4	Ipilimumab	NY-ESO-1	Metastatic melanoma	19/20	1 × 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 × 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 × 7	ICS after T-cell stimulation	SSO probing and SSP of genomic DNA	7
Total	6	7		80	157	N/A		

*Number of patients used in the retrospective analysis from the original number of patient of the clinical trials.

**Immunoassays are based on T cell stimulation with antigen-specific peptide pools and quantify the released cytokines by different techniques.

CT: Clinical trial;

SBT: Sequence Based Typing;

SSO: Sequence-Specific Oligonucleotide;

ICS: Intracellular cytokine staining;

SSP: Sequence-specific priming

[0394] 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.

The area under the ROC curve (AUC) is a measure of how well the classifier can distinguish between two diagnostic groups (CTL responder or non-responder).

[0396] The analysis unexpectedly revealed that predicted epitope presentation by multiple class I HLAs of a subject (PEPI2+, PEPI3+, PEPI4+, PEPI5+, or PEPI6), was in every case a better predictor of CTL response than epitope presentation by merely one or more HLA class I (PEPI1+, AUC=0.48, Table 12).

TABLE 12

Determination of diagnostic value of the PEPI biomarker by ROC analysis

Classifiers	AUC
PEPI1+	0.48
PEPI2+	0.51
PEPI3+	0.65

TABLE 12-continued

Determination of diagnostic value of the PEPI biomarker by ROC analysis	
Classifiers	AUC
PEPI4+	0.52
PEPI5+	0.5
PEPI6+	0.5

[0397] 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

[0398] 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).

[0399] The clinical validation demonstrated that a PEPI3+ peptide induce CTL response in an individual with 84% probability. 84% is the same value that was determined in the analytical validation of the PEPI3+ prediction, epitopes that binds to at least 3 HLAs of an individual (Table 10). These data provide strong evidences that immune responses are induced by PEPIs in individuals.

TABLE 14

Diagnostic performance characteristics of the ≥1 PEPI3+ Test (n = 81).			
Performance characteristic		Description	Result
Positive predictive value (PPV)	100%[A/(A + B)]	The likelihood that an individual that meets the ≥1 PEPI3+ threshold has antigen-specific CTL responses after treatment with immunotherapy.	84%
Sensitivity	100%[A/(A + C)]	The proportion of subjects with antigen-specific CTL responses after treatment with immunotherapy who meet the ≥1 PEPI3+ threshold.	75%
Specificity	100%[D/(B + D)]	The proportion of subjects without antigen-specific CTL responses after treatment with immunotherapy who do not meet the ≥1 PEPI3+ threshold.	55%
Negative predictive value (NPV)	100%[D/(C + D)]	The likelihood that an individual who does not meet the ≥1 PEPI3+ threshold does not have antigen-specific CTL responses after treatment with immunotherapy.	42%
Overall percent agreement (OPA)	100%[(A + D)/N]	The percentage of predictions based on the ≥1 PEPI3+ threshold that match the experimentally determined result, whether positive or negative.	70%
Fisher's exact (p)			0.01

[0400] 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.

[0401] 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

[0402] The ≥1 PEPI3+ Test was compared with a previously reported method for predicting a specific human subject's CTL response to peptide antigens.

[0403] 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 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.

[0404] 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.

[0405] 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. **3**A). Overall, the agreement between the ≥1 PEPI3+ Test and experimentally determined CD8+ T cell reactivity was 90% ($p<0.001$).

[0406] 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. **3**B). 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

[0407] 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**A-B). The sensitivity of the prediction of HLA class II restricted epitopes was 78%, since the State of Art tool predicted 84 positive responses (positive CD4+ T cell reactivity to a peptide pool for a person's DP alleles) out of 107 (sensitivity=78%). The specificity was 22% since it could rule out 7 negative responses out of 31. Overall, the agreement between HLA-restricted class II epitope prediction and CD4+ T cell reactivity was 66%, which was statistically not significant.

Example 6—The ≥1 PEPI3+ Test Predicts T Cell Responses to Full Length LPV Polypeptides

[0408] 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**).

[0409] 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

[0410] 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].

[0411] FIGS. **5**A-D and FIG. **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.

[0412] 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.

[0413] 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.

[0414] 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.

[0415] 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

[0416] An in silico human trial cohort of 433 subjects with complete 4-digit HLA class I genotype (2×HLA-A*xx:xx; 2×HLA-B*xx:xx; 2×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.

[0417] 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 $p<0.001$). Therefore the 433 patient Model Population is representative for a 16 times larger population.

[0418] 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

[0419] 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.

[0420] Twelve peptide vaccines derived from cancer antigens that induced T cell responses in a subpopulation of subjects were identified from peer reviewed publications. These peptides have been investigated in clinical trials enrolling a total of 172 patients (4 ethnicities). T cell responses induced by the vaccine peptides have been determined from blood specimens and reported. The immune response rate as the percentage of study subjects with positive T cell responses measured in the clinical trials was determined (FIG. **7**).

TABLE 17

Clinical trials conducted with peptide vaccines.

Peptide vaccines	SEQ ID NO	Source antigen	Peptide length	T cell assay	Pop. (n)	Ethnicity	Ref.
MMNLMQPKTQQTYTYD	1	JUP	16 mer	Multimer staining	18	Canadian	12
GRGSTTTNYLLDRDDYRNTSD	2	ADA17	21 mer	Multimer staining	18	Canadian	12
LKKGAADGGKLDGNAKLNRSLK	3	BAP31	22 mer	Multimer staining	18	Canadian	12
FPPKDDHTLKFLYDDNQRPYPP	4	TOP2A	22 mer	Multimer staining	18	Canadian	12
RYRKPDYTLDDGHGLLRFKST	5	Abl-2	21 mer	Multimer staining	18	Canadian	12

TABLE 17-continued

Clinical trials conducted with peptide vaccines.

Peptide vaccines	SEQ ID NO	Source antigen	Peptide length	T cell assay	Pop. (n)	Ethnicity	Ref.
QRPPFSQLHRFLADALNT	6	DDR1	18 mer	Multimer staining	18	Canadian	12
ALDQCKTSCALMQQHYDQTSCFSSP	7	ITGB8	25 mer	Multimer staining	18	Canadian	12
STAPPAHGVTSAPDTRPAPGSTAPP	8	MUC-1	25 mer	Proliferation	80	Canadian	13
YLEPGPVTA	9	gp100	9 mer	Tetramer	18	US	14
MTPGTQSPFFLLLLLTVLTVV	10	MUC-1	21 mer	Cytotoxicity	10	Israeli	15
SSKALQRPV	11	Bcr-Abl	9 mer	ELISPOT	4	US	16
RMFPNAPYL	12	WT-1	9 mer	Multimer staining	24	US	17
RMFPNAPYL (HLA-A*0201)	13	WT-1	9 mer	Cytokine staining	18	CEU	18

[0421] 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).

[0422] 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.

Peptide vaccine	SEQ ID NO	Source antigen	Response rate (Clinical Trials)	≥1 PEPI3+ Score* (Model Population)	OPA
MMNLMQPKTQQTYTYD	1	JUP	0%	22%	NA
GRGSTTTNYLLDRDDYRNTSD	2	ADA17	11%	18%	61%
LKKGAADGGKLDGNAKLNRSLK	3	BAP31	11%	7%	64%
FPPKDDHTLKFLYDDNQRPYPP	4	TOP2A	11%	39%	28%
RYRKPDYTLDDGHGLLRFKST	5	Abl-2	17%	12%	71%
QRPPFSQLHRFLADALNT	6	DDR1	17%	5%	29%
ALDQCKTSCALMQQHYDQTSCFSSP	7	ITGB8	28%	31%	90%
STAPPAHGVTSAPDTRPAPGSTAPP	8	MUC-1	20%	2%	10%
YLEPGPVTA	9	gp100	28%	4%	14%
MTPGTQSPFFLLLLLTVLTVV	10	MUC-1	90%	95%	95%
SSKALQRPV	11	Bcr-Abl	0%	0%	100%
RMFPNAPYL	12	WT-1	100%	78%	78%
RMFPNAPYL (HLA- A*0201)	13	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

[0423] 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.

[0424] 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)	Check-point 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
1 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

[0425] 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.

[0426] 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%	29%	26%
	(MultiPEPI Score)		
≥3 peptides	3%	ND	3%

[0427] 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.

[0428] 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.

[0429] 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.

[0430] 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

[0431] 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.

[0432] 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.

[0433] 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 (R2=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 restric-tion	Adm. form	Dose (mg)	Dosing schedule	Assessment time (weeks)	Ref.
IMA901 phase I	9 TAAs	Immatics	Renal cell cancer	28	CEU	A02	i.d.	0.4	8x in 10 wks	12	19
IMA901 phase II	9 TAAs	Immatics	Renal cell cancer	68	CEU	A02	i.d	0.4	7x in 5 wks then 10x 3 wks	24	19
Ipilimumab	NY-ESO-1	MSKCC	Melanoma	19	US	no	i.v.	0.3 3 10	4 x every 3 wks	24	5
HPV-SLP*	HPV-16 E6, E7	Leiden University	VIN	20	CEU	no	s.c.	0.3	3 x every 3 wks	12	9
HPV-SLP*		Leiden University	HPV-related cervical cancer	5	CEU	no	s.c.	0.3	3 x every 3 wks	12 (OR)	10
gp100 - 2 peptides*	gp100	BMS	Melanoma	136	US	A*0201	s.c.	1	4 x every 3 wks	12	28
Immucin	Muc-1	VaxilBio	Myeloma	15	Israeli	no	s.c.	0.1	6 x every 2 wks	12**	29
StimuVax	Muc-1	Merck	NSCLC	80	Canadian	no	s.c.	1	8x wkly then every 6 wks	12	13, 30
VGX-3100	HPV-16&18	Inovio	HPV-related cervical cancer	125	US	no	i.m.	6	0, 4, 12 wks	36	31
TSPP peptide vaccine	Thymidylate synthase	Siena University	CRC, NSCLC, Gallbladder carc., Breast-, Gastric cancer	21	CEU	no	s.c.	0.1 0.2 0.3	3 x 3 wks	12	32
KIF20A-66 peptide vaccine*	KIF20A	Chiba Tokushukai Hospital	Metastatic pancreatic cancer	29	Japanese	A*2402	s.c.	1 3	2 cycles 1, 8, 15, 22 days then every 2 wks	12 (OR)	33
Peptide vaccine*	3 TAAs	Kumamoto University	HNSCC	37	Japanese	A*2402	s.c.	1	8 x wkly then every 4 wks	12	34
7-peptide cocktail vaccine*	7 TAAs	Kinki University	Metastatic colorectal cancer	30	Japanese	A*2402	s.c.	1	Cycles: 5 x wkly then 1 wk rest	10 (OR)	35
GVX301*	hTERT	University Genoa	Prostate and renal cancer	14	Japanese	A02	i.d.	0.5	1, 3, 5, 7, 14, 21, 35, 63 days	12	25
MAGE-A3 Trojan*	MAGE-A3	Abramson Cancer Center	Multiple myeloma	26	US	no	s.c.	0.3	14, 42, 90, 120, 150 days	24	36
PepCan	HPV-16 E6	University of Arkansas	CIN2/3	23	US	no	i.m.	0.05 0.1 0.25 0.5	4 x 3 wks	24	37
Melanoma peptide vaccine*	Tyrosinase, gp100	University of Virginia	Melanoma	26	US	A1, A2 or A3	s.c.	0.1	6 cycles: 0, 7, 14, 28, 35, 42 days	6	27

*Montanide ISA51 VG as adjuvant

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

TABLE 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%
TSPP peptide vaccine	48%	31%	65%
KIF20A-66 peptide vaccine	26%	7%	27%

TABLE 23-continued

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

Immunotherapy	DCR	MultiPEPI Score (Predicted DCR)	Overall Percentage of Agreement
Peptide vaccine	27%	10%	37%
7-peptide cocktail vaccine	10%	9%	90%
GVX301	29%	7%	24%
MAGE-A3 Trojan	35%	10%	29%
PepCan	52%	26%	50%
Melanoma peptide vaccine	12%	6%	50%

Example 13—The Set of Multiple HLA Binding Peptides from Tumor Antigens Predicts Responders to the Checkpoint Inhibitor Immunotherapy Ipilmumab

[0434] 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.

[0435] 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.

[0436] 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].

[0437] 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 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 (FIGS. **10**A-D).

Example 14: Multiple HLA Binding Epitopes Define Patient Mutational Neoantigens

[0438] 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 data[39]. From the exome mutation data, mutations in 9,502 antigens from the 110 patients (FIG. **11**A). 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 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.

[0439] Mutational PEPI3+ neoepitopes from the published mutations were determined (FIG. **11**B and Table 24). These mutations resulted in median 16 PEPIs and 6 PEPIs neoepitopes in clinical benefit cohort and the minimal or no clinical benefit cohorts, respectively.

[0440] 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+ 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.

	Results published by Van Allen et al.		Result obtained from PEPI Test analyses (Validated epitopes and PEPIs)	
	Patients			
Parameters	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

[0441] 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 (SEQ ID NO: 87)) spanning the EGFRvIII mutation with an additional C-terminal cysteine residue.[11]

[0442] 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.

[0443] An in silico trial with the Model Population of 433 subjects with Rindopepimut sequence was conducted. 4 out of 433 subjects had PEPI3+, confirming the low immunogenicity found in the phase II study (Table 25).

TABLE 25

Results of clinical trial and in silico study

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

[0444] 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.

[0445] 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

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Example 16. Multiple HLA Binding Peptides of Individuals can Predict Immune-Toxicity

[0458] 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).

[0459] 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.

[0460] 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

[0461] This example describes the treatment of an ovarian cancer patient with a personalised immunotherapy compo-

sition, 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.

[0462] The HLA class I and class II genotype of metastatic ovarian adenocarcinoma cancer patient XYZ was determined from a saliva sample.

[0463] 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	20 mer peptides	SEQ ID NO	MAX HLA class I	MAX HLA class II
POC01_P1	AKAP4	89%	NSLQKQLQAVLQWIAASQFN	14	3	5
POC01_P2	BORIS	82%	SGDERSDEIVLTVSNSNVEE	15	4	2
POC01_P3	SPAG9	76%	VQKEDGRVQAFGWSLPQKYK	16	3	3
POC01_P4	OY-TES-1	75%	EVESTPMIMENIQELIRSAQ	17	3	4
POC01_P5	sP17	69%	AYFESLLEKREKTNFDPAEW	18	3	1
POC01_P6	WT1	63%	PSQASSGQARMFPNAPYLPS	19	4	1
POC01_P7	HIWI	63%	RRSIAGFVASINEGMTRWFS	20	3	4
POC01_P8	PRAME	60%	MQDIKMILKMVQLDSIEDLE	21	3	4
POC01_P9	AKAP-3	58%	ANSVVSDMMVSIMKTLKIQV	22	3	4
POC01_P10	MAGE-A4	37%	REALSNKVDELAHFLLRKYR	23	3	2
POC01_P11	MAGE-A9	37%	ETSYEKVINYLVMLNAREPI	24	3	4
POC01_P12a	MAGE-A10	52%	DVKEVDPTGHSFVLVTSLGL	25	3	4
POC01_P12b	BAGE	30%	SAQLLQARLMKEESPVVSWR	26	3	2

[0464] 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).

[0465] The probability that patient XYZ will express one or more of the 12 antigens is shown in FIGS. **13**A-B. AGP95=5, AGP50=7.9, mAGP=100%, AP=13.

[0466] 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.

[0467] For treatment of patient XYZ the 12 peptides were formulated as 4×3/4 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:

[0468] Diagnosis: Metastatic ovarian adenocarcinoma

Age: 51

[0469] Family anamnesis: colon and ovary cancer (mother) breast cancer (grandmother)

Tumor Pathology:

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

[0470] 2011: first diagnosis of ovarian adenocarcinoma; Wertheim operation and chemotherapy; lymph node removal

[0471] 2015: metastasis in pericardial adipose tissue, excised

[0472] 2016: hepatic metastases

[0473] 2017: retroperitoneal and mesenteric lymph nodes have progressed; incipient peritoneal carcinosis with small accompanying ascites

Prior Therapy:

[0474] 2012: Paclitaxel-carboplatin (6×)

[0475] 2014: Caelyx-carboplatin (1×)

[0476] 2016-2017 (9 months): Lymparza (Olaparib) 2×400 mg/day, oral

[0477] 2017: Hycamtin inf. 5×2.5 mg (3× one seria/month)

[0478] PIT vaccine treatment began on 21 Apr. 2017.

TABLE 27

Patient XYZ peptide treatment schedule

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

Patient' Tumor MRI Findings (Baseline Apr. 15, 2016)

[0479] Disease was confined primarily to liver and lymph nodes. The use of MRI limits detection of lung (pulmonary) metastasis

[0480] May 2016-January 2017: Olaparib treatment

[0481] Dec. 25, 2016 (before PIT vaccine treatment) There was dramatic reduction in tumor burden with confirmation of response obtained at FU2

[0482] January-March 2017—TOPO protocol (topoisomerase)

[0483] Apr. 6, 2017 FU3 demonstrated regrowth of existing lesions and appearance of new lesions leading to disease progression

[0484] Apr. 21 2017 START PIT

[0485] Jul. 21, 2017 (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

[0486] Jul. 26, 2017—CBP+Gem+Avastin

[0487] Sep. 20, 2017 (after 3 Cycles of PIT) FU5 demonstrated reversal of lesion growth and improved pancreatic/parapancreatic signal. The findings suggest pseudo progression

[0488] Nov. 28, 2017 (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 FIG. **14**.

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

[0489] 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 FIG. **15**.

TABLE 29

12 peptides for ABC breast cancer patient

BRC09 vaccine peptides	Target Antigen	Antigen Expression	20 mer peptide	SEQ ID NO	MAXHLA Class I	MAXHLA Class II
PBRC01_cP1	FSIP1	49%	ISDTKDYFMSKTLGIGRLKR	27	3	6
PBRC01_cP2	SPAG9	88%	FDRNTESLFEELSSAGSGLI	28	3	2
PBRC01_cP3	AKAP4	85%	SQKMDMSNIVLMLIQKLLNE	29	3	6
PBRC01_cP4	BORIS	71%	SAVFHERYALIQHQKTHKNE	30	3	6
PBRC01_cP5	MAGE-A11	59%	DVKEVDPTSHSYVLVTSLNL	31	3	4
PBRC01_cP6	NY-SAR-35	49%	ENAHGQSLEEDSALEALLNF	32	3	2
PBRC01 cP7	HOM-TES-85	47%	MASFRKLTLSEKVPPNHPSR	33	3	5
PBRC01_cP8	NY-BR-1	47%	KRASQYSGQLKVLIAENTML	34	3	6
PBRC01_cP9	MAGE-A9	44%	VDPAQLEFMFQEALKLKVAE	35	3	8
PBRC01_cP10	SCP-1	38%	EYEREETRQVYMDLNNNIEK	36	3	3
PBRC01_cP11	MAGE-A1	37%	PEIFGKASESLQLVEGIDVK	37	3	3
PBRC01_cP12	MAGE-C2	21%	DSESSFTYTLDEKVAELVEF	38	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).

[0490] For treatment of patient ABC the 12 peptides were formulated as 4×3 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

[0491] Diagnosis: bilateral metastatic breast carcinoma: Right breast is ER positive, PR negative, Her2 negative; Left Breast is ER, PR and Her2 negative.

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

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

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

Results

[0492] Mar. 7, 2017: Prior PIT Vaccine treatment

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

May 26 2017: After 1 cycle of PIT
Detected efficacy: 83% reduction of tumor metabolic activity (PET CT) liver, lung lymphnodes and other metastases.
Detected safety: Skin reactions
Local inflammation at the site of the injections within 48 hours following vaccine administrations

Follow Up:

[0493] BRC-09 was treated with 5 cycles of PIT vaccine. She was feeling very well and she refused a PET CT examination in September 2017. In November she had symptoms, PET CT scan showed progressive disease, but she refused all treatments. In addition, her oncologist found out that she did not take Palbocyclib since spring/summer. Patient ABC passed away in January 2018.

[0494] The combination of palbocyclib and the personalised vaccine was likely to have been responsible for the remarkable early response observed following administration of the vaccine. Palbocyclib has been shown to improve the activity of immunotherapies by increases CTA presen

tation by HLAs and decreasing the proliferation of Tregs: (Goel et al. Nature. 2017:471-475). The PIT vaccine may be used as add-on to the state-of-art therapy to obtain maximal efficacy.

Example 19—Personalised Immunotherapy Composition for Treatment of Patient with Late Stage Metastatic Breast Cancer

[0495] Patient BRC05 was diagnosed with inflammatory breast cancer on the right with extensive lymphangiosis carcinomatose. Inflammatory breast cancer (IBC) is a rare, but aggressive form of locally advanced breast cancer. It's called inflammatory breast cancer because its main symptoms are swelling and redness (the breast often looks inflamed). Most inflammatory breast cancers are invasive ductal carcinomas (begin in the milk ducts). This type of breast cancer is associated with the expression of oncoproteins of high risk Human Papilloma Virus. Indeed, HPV16 DNA was diagnosed in the tumor of this patient.

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

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

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

[0496] 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

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

[0497] 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

[0498] 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.

Example 20—Personalised Immunotherapy Composition for Treatment of Patient with Early Stage Metastatic Breast Cancer

[0499] HISTORY: In 2011 left breast sector excision due to neoplasm. Treatment: aromatase inhibitor and lumbar spine irradiation (osseal mets).

[0500] 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 righ 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	MAXHLA CD8	MAXHLA CD4
PBRC04_P1	SPAG9	88%	XXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P2	AKAP4	85%	XXXXXXXXXXXXXXXXXXXX	4	4
PBRC04_P3	BORIS	71%	XXXXXXXXXXXXXXXXXXXX	3	2
PBRC04_P4	MAGE-A11	59%	XXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P6	NY-SAR-35	49%	XXXXXXXXXXXXXXXXXXXX	3	5
PBRC04_P7	FSIP1	49%	XXXXXXXXXXXXXXXXXXXX	3	6
PBRC04_P8	NY-BR-1	47%	XXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P10	LDHC	35%	XXXXXXXXXXXXXXXXXXXX	3	5
PBRC04_P11	GATA-3	31%	XXXXXXXXXXXXXXXXXXXX	3	1
PBRC04_P13	Survivin	71%	XXXXXXXXXXXXXXXXXXXX	3	2
PBRC04_P14	MAGE-C1	12%	XXXXXXXXXXXXXXXXXXXX	3	8
PBRC04_P15	PRAME	55%	XXXXXXXXXXXXXXXXXXXX	3	5

[0501] The patient obtained 2 cycles of PIT vaccine.

Example 21—Characterization of Toxicity—immunoBLAST

[0502] 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.

[0503] PolyPEPI1018 contains six 30-mer polypeptides. Each polypeptide consists of two 15-mer peptide fragments derived from antigens expressed in CRC. Neoepitopes might be generated in the joint region of the two 15-mer peptides and could induce undesired T cell responses against healthy cells (autoimmunity). This was assesses using the immunoBLAST methodology.

[0504] 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.

[0505] As shown in FIG. **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).

[0506] 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.

[0507] 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

		Epitope & PEPI3+ binding in 433 Subjects of the Model Population								
PolyPEPI		Epitope Binding (1 x HLA)								
1018		SEQ					PEPI3+ binding (3 x HLA)			
Peptide ID:	Potential Neoepitope	ID NO	Sub#	Sub %	NeoEPI	NeoEPI count	Sub#	Sub %	NeoPEPI	NeoPEPI count
CRC-P1	QFPVSEGKS	39	0	0.0%			0	0.0%		3
	FPVSEGKSR	40	160	37.0%	X		1	0.2%	X	
	PVSEGKSRY	41	150	34.6%	X		0	0.0%		
	VSEGKSRYR	42	194	44.8%	X	7	1	0.2%	X	
	SEGKSRYRA	43	113	26.1%	X		0	0.0%		
	EGKSRYRAQ	44	77	17.8%	X		0	0.0%		
	GKSRYRAQR	45	37	8.5%	X		0	0.0%		
	KSRYRAQRF	46	337	77.8%	X		33	7.6%	X	
CRC-P2	IELKHKART	47	32	7.4%	X	7	0	0.0%		1
	ELKHKARTA	48	63	14.5%	X		0	0.0%		
	LKHKARTAK	49	59	13.6%	X		0	0.0%		
	KHKARTAKK	50	166	38.3%	X		1	0.2%	X	
	HKARTAKKV	51	0	0.0%			0	0.0%		
	KARTAKKVR	52	70	16.2%	X		0	0.0%		
	ARTAKKVRR	53	134	30.9%	X		0	0.0%		
	RTAKKVRRA	54	41	9.5%	X		0	0.0%		
CRC-P3	EFSMQGLKD	55	0	0.0%		5	0	0.0%		1
	FSMQGLKDE	56	188	43.4%	X		0	0.0%		
	SMQGLKDEK	57	138	31.9%	X		0	0.0%		
	MQGLKDEKV	58	16	3.7%	X		0	0.0%		
	QGLKDEKVA	59	0	0.0%			0	0.0%		
	GLKDEKVAE	60	0	0.0%			0	0.0%		
	LKDEKVAEL	61	186	43.0%	X		3	0.7%	X	
	KDEKVAELV	62	51	11.8%	X		0	0.0%		
CRC-P6	LLALMVGLK	63	252	58.2%	X	7	0	0.0%		1
	LALMVGLKD	64	86	19.9%	X		0	0.0%		
	ALMVGLKDH	65	65	15.0%	X		0	0.0%		
	LMVGLKDHR	66	97	22.4%	X		0	0.0%		
	MVGLKDHRI	67	67	15.5%	X		0	0.0%		
	VGLKDHRIS	68	0	0.0%			0	0.0%		
	GLKDHRIST	69	4	0.9%	X		0	0.0%		
	LKDHRISTF	70	195	45.0%	X		5	1.2%	X	
CRC-P7	PALFKENRS	71	0	0.0%		5	0	0.0%		1
	ALFKEN RSG	72	0	0.0%			0	0.0%		
	LFKENRSGA	73	41	9.5%	X		0	0.0%		
	FKENRSGAV	74	114	26.3%	X		0	0.0%		
	KENRSGAVM	75	261	60.3%	X		0	0.0%		
	ENRSGAVMS	76	0	0.0%			0	0.0%		
	NRSGAVMSE	77	227	52.4%	X		0	0.0%		
	RSGAVMSER	78	197	45.5%	X		2	0.5%	X	
CRC-P8	AVLTKKFQK	79	181	41.8%	X	7	0	0.0%		3
	VLTKKFQKV	80	208	48.0%	X		2	0.5%	X	
	LTKKFQKVN	81	0	0.0%			0	0.0%		
	TKKFQKVNF	82	25	5.8%	X		0	0.0%		
	KKFQKVNFF	83	250	57.7%	X		12	2.8%	X	
	KFQKVNFFF	84	273	63.0%	X		23	5.3%	X	
	FQKVNFFFE	85	163	37.6%	X		0	0.0%		
	QKVNFFFER	86	110	25.4%	X		0	0.0%		

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

REFERENCES

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Tyr Leu Pro Ser
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Asn Thr Met Leu
20

<210> SEQ ID NO 35
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: ABC 9

<400> SEQUENCE: 35

Val Asp Pro Ala Gln Leu Glu Phe Met Phe Gln Glu Ala Leu Lys Leu
1 5 10 15

Lys Val Ala Glu
20

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<210> SEQ ID NO 36
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: ABC 10

<400> SEQUENCE: 36

Glu Tyr Glu Arg Glu Glu Thr Arg Gln Val Tyr Met Asp Leu Asn Asn
1 5 10 15

Asn Ile Glu Lys
20

<210> SEQ ID NO 37
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: ABC 11

<400> SEQUENCE: 37

Pro Glu Ile Phe Gly Lys Ala Ser Glu Ser Leu Gln Leu Val Phe Gly
1 5 10 15

Ile Asp Val Lys
20

<210> SEQ ID NO 38
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: ABC 12

<400> SEQUENCE: 38

Asp Ser Glu Ser Ser Phe Thr Tyr Thr Leu Asp Glu Lys Val Ala Glu
1 5 10 15

Leu Val Glu Phe
20

<210> SEQ ID NO 39
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 1

<400> SEQUENCE: 39

Gln Phe Pro Val Ser Glu Gly Lys Ser
1 5

<210> SEQ ID NO 40
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 2

<400> SEQUENCE: 40

Phe Pro Val Ser Glu Gly Lys Ser Arg
1 5

<210> SEQ ID NO 41
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 3

<400> SEQUENCE: 41

Pro Val Ser Glu Gly Lys Ser Arg Tyr
1 5

<210> SEQ ID NO 42
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 4

<400> SEQUENCE: 42

Val Ser Glu Gly Lys Ser Arg Tyr Arg
1 5

<210> SEQ ID NO 43
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 5

<400> SEQUENCE: 43

Ser Glu Gly Lys Ser Arg Tyr Arg Ala
1 5

<210> SEQ ID NO 44
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 6

<400> SEQUENCE: 44

Glu Gly Lys Ser Arg Tyr Arg Ala Gln
1 5

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<210> SEQ ID NO 45
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 7

<400> SEQUENCE: 45

Gly Lys Ser Arg Tyr Arg Ala Gln Arg
1 5

<210> SEQ ID NO 46
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P1 8

<400> SEQUENCE: 46

Lys Ser Arg Tyr Arg Ala Gln Arg Phe
1 5

<210> SEQ ID NO 47
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 1

<400> SEQUENCE: 47

Ile Glu Leu Lys His Lys Ala Arg Thr
1 5

<210> SEQ ID NO 48
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 2

<400> SEQUENCE: 48

Glu Leu Lys His Lys Ala Arg Thr Ala
1 5

<210> SEQ ID NO 49
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 3

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<400> SEQUENCE: 49

Leu Lys His Lys Ala Arg Thr Ala Lys
1 5

<210> SEQ ID NO 50
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 4

<400> SEQUENCE: 50

Lys His Lys Ala Arg Thr Ala Lys Lys
1 5

<210> SEQ ID NO 51
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 5

<400> SEQUENCE: 51

His Lys Ala Arg Thr Ala Lys Lys Val
1 5

<210> SEQ ID NO 52
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 6

<400> SEQUENCE: 52

Lys Ala Arg Thr Ala Lys Lys Val Arg
1 5

<210> SEQ ID NO 53
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 7

<400> SEQUENCE: 53

Ala Arg Thr Ala Lys Lys Val Arg Arg
1 5

<210> SEQ ID NO 54
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P2 8

<400> SEQUENCE: 54

Arg Thr Ala Lys Lys Val Arg Arg Ala
1 5

<210> SEQ ID NO 55
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 1

<400> SEQUENCE: 55

Glu Phe Ser Met Gln Gly Leu Lys Asp
1 5

<210> SEQ ID NO 56
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 2

<400> SEQUENCE: 56

Phe Ser Met Gln Gly Leu Lys Asp Glu
1 5

<210> SEQ ID NO 57
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 3

<400> SEQUENCE: 57

Ser Met Gln Gly Leu Lys Asp Glu Lys
1 5

<210> SEQ ID NO 58
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 4

<400> SEQUENCE: 58

Met Gln Gly Leu Lys Asp Glu Lys Val
1 5

<210> SEQ ID NO 59
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 5

<400> SEQUENCE: 59

Gln Gly Leu Lys Asp Glu Lys Val Ala
1 5

<210> SEQ ID NO 60
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 6

<400> SEQUENCE: 60

Gly Leu Lys Asp Glu Lys Val Ala Glu
1 5

<210> SEQ ID NO 61
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 7

<400> SEQUENCE: 61

Leu Lys Asp Glu Lys Val Ala Glu Leu
1 5

<210> SEQ ID NO 62
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P3 8

<400> SEQUENCE: 62

Lys Asp Glu Lys Val Ala Glu Leu Val
1 5

<210> SEQ ID NO 63
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 1

<400> SEQUENCE: 63

Leu Leu Ala Leu Met Val Gly Leu Lys
1 5

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<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 2

<400> SEQUENCE: 64

Leu Ala Leu Met Val Gly Leu Lys Asp
1 5

<210> SEQ ID NO 65
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 3

<400> SEQUENCE: 65

Ala Leu Met Val Gly Leu Lys Asp His
1 5

<210> SEQ ID NO 66
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 4

<400> SEQUENCE: 66

Leu Met Val Gly Leu Lys Asp His Arg
1 5

<210> SEQ ID NO 67
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 5

<400> SEQUENCE: 67

Met Val Gly Leu Lys Asp His Arg Ile
1 5

<210> SEQ ID NO 68
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 6

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<400> SEQUENCE: 68

Val Gly Leu Lys Asp His Arg Ile Ser
1 5

<210> SEQ ID NO 69
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 7

<400> SEQUENCE: 69

Gly Leu Lys Asp His Arg Ile Ser Thr
1 5

<210> SEQ ID NO 70
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P6 8

<400> SEQUENCE: 70

Leu Lys Asp His Arg Ile Ser Thr Phe
1 5

<210> SEQ ID NO 71
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 1

<400> SEQUENCE: 71

Pro Ala Leu Phe Lys Glu Asn Arg Ser
1 5

<210> SEQ ID NO 72
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 2

<400> SEQUENCE: 72

Ala Leu Phe Lys Glu Asn Arg Ser Gly
1 5

<210> SEQ ID NO 73
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 3

<400> SEQUENCE: 73

Leu Phe Lys Glu Asn Arg Ser Gly Ala
1 5

<210> SEQ ID NO 74
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 4

<400> SEQUENCE: 74

Phe Lys Glu Asn Arg Ser Gly Ala Val
1 5

<210> SEQ ID NO 75
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 5

<400> SEQUENCE: 75

Lys Glu Asn Arg Ser Gly Ala Val Met
1 5

<210> SEQ ID NO 76
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 6

<400> SEQUENCE: 76

Glu Asn Arg Ser Gly Ala Val Met Ser
1 5

<210> SEQ ID NO 77
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 7

<400> SEQUENCE: 77

Asn Arg Ser Gly Ala Val Met Ser Glu
1 5

<210> SEQ ID NO 78
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P7 8

<400> SEQUENCE: 78

Arg Ser Gly Ala Val Met Ser Glu Arg
1 5

<210> SEQ ID NO 79
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 1

<400> SEQUENCE: 79

Ala Val Leu Thr Lys Lys Phe Gln Lys
1 5

<210> SEQ ID NO 80
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 2

<400> SEQUENCE: 80

Val Leu Thr Lys Lys Phe Gln Lys Val
1 5

<210> SEQ ID NO 81
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 3

<400> SEQUENCE: 81

Leu Thr Lys Lys Phe Gln Lys Val Asn
1 5

<210> SEQ ID NO 82
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 4

<400> SEQUENCE: 82

Thr Lys Lys Phe Gln Lys Val Asn Phe
1 5

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<210> SEQ ID NO 83
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 5

<400> SEQUENCE: 83

Lys Lys Phe Gln Lys Val Asn Phe Phe
1 5

<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 6

<400> SEQUENCE: 84

Lys Phe Gln Lys Val Asn Phe Phe Phe
1 5

<210> SEQ ID NO 85
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 7

<400> SEQUENCE: 85

Phe Gln Lys Val Asn Phe Phe Phe Glu
1 5

<210> SEQ ID NO 86
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CRC-P8 8

<400> SEQUENCE: 86

Gln Lys Val Asn Phe Phe Phe Glu Arg
1 5

<210> SEQ ID NO 87
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 87

Leu Glu Glu Lys Lys Gly Asn Tyr Val Val Thr Asp His Cys
1 5 10

1. A human subject-specific pharmaceutical composition for treatment of a disease or disorder in a specific human subject, comprising:

(a) at least two different polypeptides, each of the at least two different polypeptides comprising 10-50 amino acids 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 epitopes of each of the at least two polypeptides are different; and

(b) a pharmaceutically-acceptable adjuvant.

2. The human subject-specific pharmaceutical composition of claim **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 claim **1**, comprising 3-40 different polypeptides.

4. The human subject-specific pharmaceutical composition of claim **1**, wherein the T cell epitope that binds at least three HLA class I molecules of the subject comprises 7 to 17 amino acids.

5. The human subject-specific pharmaceutical composition of claim **1**, wherein the T cell epitopes of the at least two different polypeptides are from a single antigen.

6. The human subject-specific pharmaceutical composition of claim **1**, wherein the T cell epitopes of the at least two different polypeptides are from two or more different antigens.

7. The human subject-specific pharmaceutical composition of claim **5**, 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, 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.

8. The human subject-specific pharmaceutical composition of claim **7**, wherein the cancer cell is from the subject.

9. The human subject-specific pharmaceutical composition of claim **5**, wherein the antigen is selected from Tables 2 to 7.

10. The human subject-specific pharmaceutical composition of claim **1**, wherein the at least two 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 the corresponding antigen.

11. The human subject-specific pharmaceutical composition of claim **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 the corresponding antigen.

12. The human subject-specific pharmaceutical composition of claim **1**, wherein two of the at least two polypeptides are arranged end to end or overlapping in a joined polypeptide.

13. The human subject-specific pharmaceutical composition of claim **12**, comprising two or more different joined polypeptides, wherein the two or more different joined polypeptides comprise different T cell epitopes.

14. The human subject-specific pharmaceutical composition of claim **13**, wherein the joined polypeptides do not substantially comprise 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).

15. The human subject-specific pharmaceutical composition of claim **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

(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 claim **1**, further comprising a pharmaceutically acceptable diluent, carrier, preservative, or combination thereof.

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

18.-**20**. (canceled)

21. A human subject-specific pharmaceutical composition comprising:

a nucleic acid molecule expressing two or more polypeptides, each polypeptide comprising 10-50 amino acids 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 two or more polypeptides comprise different T cell epitopes, wherein the two or more polypeptides do not comprise amino acid sequences that are adjacent to each other in a corresponding antigen.

22.-**47**. (canceled)

48. A method of treating a cancer in a specific human subject in need thereof comprising:

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

the at least one polypeptide comprising 10-50 amino acids comprising a first 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 first T cell epitope is from an antigen that is specific for the cancer.

49-**54**. (canceled)

55. The method of claim **48**, wherein the antigen is listed in Table 2.

56.-**81**. (canceled)

* * * * *