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(54) Title: PEPTIDE COMBINATIONS AND USE THEREOF IN TREATING CEDAR POLLEN ALLERGY

(57) Abstract: The present invention provides peptide combinations for use in immunotherapy for the treatment of allergy to cedar and cypress pollen, e.g. Japanese cedar pollen and related cross-reactive pollen from members of the cypress family (Cupressaceae). The peptide combinations, which are designed to have a high worldwide HLA coverage, comprise at least three different peptides, including at least one Cry j 1 peptide and at least one Cry j 2 peptide.



PEPTIDE COMBINATIONS AND USE THEREOF IN TREATING CEDAR POLLEN ALLERGY**FIELD OF THE INVENTION**

The present invention relates to T cell epitope-containing peptides/polypeptides derived from allergens of the genus *Cryptomeria japonica* and uses of such peptides for modulating an immune response, for treating an allergic response and/or for inducing or promoting immunological tolerance, mixes thereof and for use in diagnostic methods and kits.

BACKGROUND OF THE INVENTION

Allergy caused by pollen of "Japanese cedar" (*Cryptomeria japonica*) is a significant problem in some parts of the world, in particular in Japan, where reforestation policies after World War II resulted in the planting of large forests of Japanese cedar and Japanese cypress that now produce large amounts of pollen. The main Japanese cedar allergens responsible for the allergic reaction are referred to as Cry j 1 and Cry j 2, although other Cry j allergens have been described.

One possible approach for treatment of Japanese cedar allergy is the use of allergen-specific immunotherapy based on pollen extract, which is administered to a subject over an extended period of time to induce a state of "tolerance" in the subject. The mechanism of action is thought to involve induction of IgG inhibitory antibodies, suppression of mast cell/basophil reactivity, suppression of T-cell responses, the promotion of T-cell anergy, and/or clonal deletion, and in the long term, decrease in the levels of allergen specific IgE.

Unfortunately, allergen-specific immunotherapy bears the risk of IgE-mediated adverse events, including serious anaphylactic responses. In recent years, it has been suggested to use smaller fragments derived from allergens, typically the major allergens, where the smaller fragments (peptides) contain one or more epitopes recognized by T cells regulating the allergic reaction. This concept has been termed peptide immunotherapy (PIT), in which repeated doses of the peptide are administered to a subject.

More specifically, on the molecular level, peptides are bound by Human Leucocyte Antigen (HLA) class II on the surface of Antigen Presenting Cells (APC). This peptide-HLA complex is then recognized by specific T-cell receptors on the cell surface of T-cells, which upon interaction with the APCs become activated. A major difference between peptide-based immunotherapy and therapies based on full-length allergens is that this interaction is thought to occur without a concomitant

antibody-mediated "danger signal" being elicited. This is thought to drive the T-cell response in a more tolerogenic direction.

Peptide-based immunotherapy (PIT) represents a potentially attractive alternative to allergen extracts, as it may provide a more favourable safety/tolerability profile and a significantly shorter treatment regimen than existing therapies. It is believed that, in contrast to therapies based on intact allergens, PIT solely addresses the T-cell compartment of the immune system without engaging existing antibody responses. Consequently, no IgE-mediated adverse events are expected such as those that are often seen when treating allergy with traditional allergen-based immunotherapy products (sometimes referred to as "allergy vaccines"). Peptide immunotherapies are today in clinical development and seem to have a safety profile that is similar to or better than whole allergen based immunotherapies.

A shortcoming of using peptides (T-cell epitopes), however, is associated with the restriction of each peptide to only bind a subset of the naturally occurring HLA Class II molecules within the human population. A mix of several peptides covering different HLA Class II molecules is therefore necessary to generate a broadly acting immunotherapy allergy treatment. As this repertoire of HLA Class II molecules varies from one person to another and from one ethnic population to another, it is challenging to provide peptide-based immunotherapies that can be effective in allergic subjects of any ethnic origin and any geographic region in the world unless numerous peptides are included in the immunotherapy product. Taking into consideration the enormous costs and risks in the clinical development of new allergy immunotherapy products and the increasing demands from regulatory bodies to meet high standards for CMC (chemistry, manufacturing and controls), toxicity testing, dose justification, safety and efficacy trials, it is desirable to provide peptide immunotherapy products that contain as few peptides as possible, but which at the same time are able to treat the majority of Japanese cedar pollen allergic subjects in any population using the same immunotherapy product.

T cell epitope containing peptides from Cry j 1 and Cry j 2 have previously been described in the art (see e.g. Sone et al 2009, Sone et al 1998, WO 95/27786, US 2005/0152927 and US2006/0188446, EP0700929), wherein combination of peptides derived from either Cry j 1 or Cry j 2 have been suggested useful in immunotherapy.

Despite these there is a need for improved combinations of peptides comprising peptides from both major allergen group 1 and 2 which are suitable as a pharmaceutical drug.

SUMMARY OF THE INVENTION

It has been found by the present inventors that it is possible to assemble peptide combinations comprising or consisting of a few peptides, such as three, four, five or six peptides, wherein the peptides in common cover a high fraction of the HLA Class II allele repertoire of a worldwide population, including particularly a Japanese population, produce a T cell response in a high fraction of a population allergic to Japanese cedar pollen and which importantly also are suitable for being used as a vaccine for treating allergy in that the peptides of the composition are found satisfactorily soluble in aqueous solution.

Such compositions (peptide combinations) may be assembled by

- first providing a set of T cell epitope containing peptides of the most important allergens of Japanese cedar, Cry j 1 and Cry j 2 (for example as disclosed in Example 1),
- then select the most dominant peptides, e.g. those peptides having a T cell responder coverage of at least 20% of a population,
- then estimate the HLA Class II allele worldwide coverage of each individual peptide (for example as disclosed in Example 5 and select peptides having high coverage, for example above 40%
- then verify by in vitro HLA Class II allele binding assay the estimated HLA Class II allele world-wide coverage, for example as described in Example 4,
- then experimentally or by prediction tools select peptides with satisfactorily aqueous solubility and make modified peptides with improved solubility, for example as described in Example 3,
- and then finally assembling peptide combinations, wherein the peptides in common have a high HLA Class II allele repertoire of a worldwide population, for example above 80% of a world-wide population or a Japanese population, or produces a T cell response in above 80% of a worldwide population or a Japanese population, for example as described in Example 6. Additional parameters which may be considered in the desire of providing optimal peptide combinations may be to estimate the average number of responding peptides per individual of a population because a peptide combination that in average produces a T cell response in an individual with two peptides is considered superior over a peptide combination that in average produces a T cell response with 1 peptide. Therefore, more optimal peptide compositions are considered to have a T cell response coverage of above 80% and a Responding peptides per donor of about 1.2 or above.

Notably, the present inventors have provided peptide combinations consisting as few as three peptides, which comply with the above-mentioned criteria. For example peptide mix numbered 242 in Table 7a have a T cell response coverage of 100% and responding peptides per donor of 1.4 as shown in Table 7b (Measures and B). Further peptide combinations are provided in Table 7a throughout Table 11b.

Thus, there is provided a combination of peptides (herein also named "peptide combination" or "peptide mix") for use as an "allergy vaccine" in the treatment of allergy to Japanese cedar, which combination is suitable for addressing the immune system of the majority of the world population, especially the Japanese population.

It appears that such superior peptide combinations may be assembled using a limited number of distinct peptides derived from different regions of the Cry j 1 or Cry j 2 allergen. That is to say that the peptides do not have sequence overlap, or if present, then only with a few number of amino acid residues that would not give rise to the presence of a common T cell epitope. For example, one distinct peptide overlap with few amino acid residues of another distinct peptide such as overlapping with less than 9, 8, 7, 6, 5, amino acid residues.

Therefore, the present invention relates in a first aspect, a composition comprising three peptides, which independently are 13 to 25 amino acid residues in length, wherein a first peptide is selected from group a) comprising peptides of either formula I or I*, a second peptide is selected from group b) comprising peptides of either formula II or II* and a third peptide is selected from group c) comprising peptides of group a) and b), wherein

- a peptide of formula I has an amino acid sequence defined by: a-A1-C1-B1-b
- a peptide of formula I* has an amino acid sequence defined by: a-A1-C1*-B1-b
- a peptide of formula II has an amino acid sequence defined by: a-A2-C2-B2-b
- a peptide of formula II* has an amino acid sequence defined by: a-A2-C2*-B2-b

and wherein

- C1 is an amino acid sequence selected from any one of SEQ ID NOs: 77, 48, 56 and 66,
- C1* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C1 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C1* is shorter than C1;
- C2 is an amino acid sequence selected from any one of SEQ ID NOs: 97, 107 and 125;
- C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C2* is shorter than C2;

- A1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- B1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- 5 - A2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- B2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

and wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

- As explained, a peptide composition of 3 peptides, may be extended by further peptides to improve the T cell response coverage to above 80%, such as above 90% and with more responding peptides per donor, such as above 1.7, such as above 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4 or above. For example, the present inventors have found a five peptide combination (Mix 153) having T cell response coverage of 100% and with responding peptides per donor of 2 (Tables 9a and b in combination), whereas a six peptide mix may be even better, for example the six peptide combination numbered 263 having T cell response coverage of 100% and with responding peptides per donor of 2.6 (Tables 10a and 10b in combination),

- Therefore, further peptides may be included and a further aspect relates to a composition comprising a first, second and third peptide, which also may comprise a fourth, fifth, sixth and/or further peptide, which peptide(s) independently are 13 to 25 amino acid residues in length, wherein any one of the fourth, fifth, sixth or further peptide is of either formula III or III* or formula IV or IV*, wherein

- a peptide of formula III has an amino acid sequence defined by: a-A3-C3-B3-b
- a peptide of formula III* has an amino acid sequence defined by: a-A3-C3*-B3-b
- a peptide of formula IV has an amino acid sequence defined by: a-A4-C4-B4-b
- 30 - a peptide of formula IV* has an amino acid sequence defined by: a-A4-C4*-B4-b

and wherein

- C3 is an amino acid sequence selected from any one of SEQ ID NOs: 49, 59, or 64,
- C3* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C3 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C3* is shorter than C3;

- C4 is an amino acid sequence selected from any one of SEQ ID NOs: 14, 98, 100 or 113,
- C4* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C4 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C4* is shorter than C4;

- 5 - A3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- B3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- 10 - A4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- B4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);
- 15 and wherein C3, C3*, C4, or C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO as C1, C1*, C2, C2*, C3 or C3* or C4 or C4* as any other peptide in the composition.

20 In a further aspect the invention provides a pharmaceutical composition comprising a composition as defined herein.

25 The invention provides in another aspect a method for treating allergy to cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a composition as defined herein.

30 In further aspects the invention provides a composition as defined herein for use in the treatment of allergy to cedar and cypress pollen, e.g. Japanese cedar pollen allergy, in a subject in need thereof, and a composition as defined herein for the preparation of a medicament for the treatment of allergy to cedar and cypress pollen, e.g. Japanese cedar pollen allergy, in a subject in need thereof.

The invention provides in a further aspect, a method for relieving one or more symptoms of an immune response triggered by cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a composition described herein.

The invention provides in a further aspect, a method for inducing immunological tolerance against cedar and cypress pollen, e.g. Japanese cedar pollen, comprising administering to the subject a therapeutically effective amount of a composition described herein.

In further aspects, the invention relates to compositions as defined herein for use in a method defined herein, e.g. a composition as defined herein for use in relieving an immune response triggered by cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof; for use in relieving one or more symptoms of an immune response triggered by cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof; and/or for inducing immunological tolerance against cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof.

In further aspects, the invention relates to the use of a composition as defined herein for the preparation of a medicament for use in a method defined herein, e.g. the use of a composition as defined herein for the preparation of a medicament for use in relieving an immune response triggered by cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof; for use in relieving one or more symptoms of an immune response triggered by cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof; and/or for inducing immunological tolerance against cedar and cypress pollen, e.g. Japanese cedar pollen, in a subject in need thereof.

In a still further aspect the invention provides an *in vitro* method of determining whether T cells of a subject in need of treatment recognize a composition as defined herein, comprising contacting T cells obtained from the subject with the peptide combination or single peptides thereof and detecting whether the T cells are stimulated by the peptides.

In still further aspects, the invention relates to a kit comprising a compartment and instructions, wherein the compartment comprises a composition described herein and wherein the instructions are for use in treating allergy to cedar and cypress pollen, e.g. Japanese cedar pollen,.

In still further aspects, the invention relates to a method of determining whether T cells of a subject in need of treatment recognize a composition as defined herein, comprising contacting T cells obtained from the subject with said composition or a single peptide thereof and detecting whether the T cells are stimulated by said composition or single peptide.

In still another aspect, the invention relates to a diagnostic kit comprising a composition defined herein.

DETAILED DISCLOSURE OF THE INVENTION

Definitions

The term "peptide" as used herein denotes an individual (e.g. isolated) amino acid molecule having a sequence length of about 13 to 25 amino acid residues.

- 5 As used herein an "epitope" refers to a region or part of an antigen, such as a peptide disclosed herein, that elicits an immune response when administered to a subject. An epitope may be a T cell epitope, i.e., an epitope that elicits, stimulates, induces, promotes, increases or enhances a T cell activity, function or response. For example a Th2 cell epitope. Any peptide or combination of peptides of interest can be analyzed to determine whether they include at least one T cell epitope
10 using any number of assays (e.g. T cell proliferation assays, lymphokine secretion assays, T cell non-responsiveness studies, etc.).

- The term "allergen" refers to an antigen which elicits, induces, stimulates, or enhances an immune response by a cell of the immune system of an exposed animal (e.g., human). An antigen is an allergen when the specific immune response is the development of enhanced sensitivity or a
15 hypersensitivity to the antigen, but the antigen itself is not typically innately harmful. An allergen is therefore a particular type of antigen that can cause development of enhanced or increased sensitivity or hypersensitivity in a subject. For example, an allergen can elicit production of IgE antibodies in predisposed subjects. An allergen is an allergenic protein.

- A "region" of an allergen is to be understood as a stretch of contiguous amino acids in the allergen.
20 When one peptide is derived from the same region of an allergen as another peptide, it is to be understood as both peptides aligning to the same region of that allergen.

If no other meaning is given specifically the term "T cell response" refers to an interleukin or a proliferation response by a T cell. It may be determined as explained in Example 1. It may in some instances be referred to simply as a "response" to a peptide.

- 25 The term "allergic response" is intended to refer to the hypersensitive immune reaction to a normally innocuous environmental substance known as an allergen. The most common mechanism of allergic reactions is the binding of IgE to the surface of mast cells, which causes asthma, hay fever and other common allergic reactions

- The term "subject" or "individual" is intended to refer to a mammal, in particular to a human being
30 or a person, but the individual may also be an animal, such as a cat, dog, horse.

When stating that C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide is herein meant that a third peptide is not composed from the same SEQ ID NO selected for C1 of the first peptide and not composed from the same SEQ ID NO selected for C2 of the second peptide. Thus, a first, second and third peptide is considered distinct in relation to each other. Furthermore, a fourth, fifth and sixth and any further peptide in a composition is considered distinct in relation to each other and any other peptide of the composition.

When stating that an amino acid sequence is "defined from" a reference amino acid sequence (e.g. C1, C2, C3 or C4) is herein meant that the amino acid sequence relates to the reference amino acid sequence if it is either shorter (e.g. a fragment of C1, C2, C3 or C4) or longer (e.g. extended by amino acids of the source allergen (e.g. SEQ ID NO: 1 or 3) or that at most 3 amino acid substitutions is introduced in C1, C2, C3 or C4. For instance, if a reference amino acid sequence has the amino acid sequence ACGTTVSLHISTVDD, then the following sequences are, among other, "defined from" this reference amino acid sequence: CGHHVSLHISTV, ACGTTVPSLHISTVDD, ECGTTVSLHISTVDE, STVSLHISTVDP .

The term "cross reactive" or "cross reactivity" is in general the ability of a T cell receptor (of an individual) to recognize different antigenic (poly)peptides. Herein the cross reactivity is focused on the ability of a T cell line to respond to a peptide of an allergen which is considered to be a homologue to an allergen used to establish the given T cell line. Specifically, T cell lines established on Cedar pollen allergens (e.g. Cry j 1 and Cry j 2) are used to test peptides derived from allergens of species considered to be homologues of Cry j 1 and Cry j 2, e.g. Cha o 1 and Cha o 2. A peptide eliciting a T cell response in such a T cell line is considered to also induce a T cell response in an individual sensitized Cha o 1 and Cha o 2.

The human leukocyte antigen (HLA) system is the locus of genes that encode for proteins on the cell surface that present the antigen to T cells and are termed as MHC (Major histocompatibility complex) at protein level. The HLA term has been commonly used in the patent which should in general be understood as MHC class II molecules.

HLA alleles are referred to herein using mostly a simpler notation, such as DRB1_0101 or DPA10102-DPB10101, respectively instead of the official HLA nomenclature, as presented at the web site "HLA Nomenclature" <[url:http://hla.alleles.org/](http://hla.alleles.org/)>. The amino acid sequence of an expressed HLA allele can be identified as HLA-X*YY:ZZ where X denotes a specific locus, e.g. the DRB1 locus. YY is a two digit number referring to the allele group, formerly defined by the serotype. ZZ is a two or three digit number (herein always two digits) defining the specific HLA protein. Thus a specific beta chain may be referred to as e.g., HLA-DRB1*01:01, and a specific

alpha-beta chain pair may be denoted as HLA-DPA1*02:01-HLA-DPB1*01:01. In the terminology used herein, that same specific alpha-beta chain pair may alternatively be denoted as HLA-DPA10201-HLA-DPB10101.

"pI" refers to the isoelectric point of a peptide or of a polypeptide. It may be calculated theoretically using programmes readily available on the internet or it may be determined experimentally according to known methods. Herein the pI's used are theoretically determined unless it is mentioned to be experimentally determined.

The "pI range of the peptides of the composition" refers to the span between the highest and the lowest pI of all peptides of a composition (peptide combination).

As used herein an "epitope" refers to a region or part of an antigen, such as a peptide disclosed herein, that elicits an immune response when administered to a subject. An epitope may be a T cell epitope, i.e. an epitope that elicits, stimulates, induces, promotes, increases or enhances a T cell activity, function or response, for example a Th2 cell epitope. Any peptide or a combination of peptides of interest can be analyzed to determine whether they include at least one T cell epitope using any number of assays (e.g. T cell proliferation assays, lymphokine secretion assays, T cell non-responsiveness studies, etc.).

Compositions

As mentioned, the present inventors have provided peptide combinations composed of a limited set of peptides. The following Table A lists such peptides considered parent peptides as indicated by an asterisk(*) in Table A and denoted C1, C2, C3 or C4 in embodiments disclosed herein, as well as peptides considered variants thereof. For example, a variant may be designed according to the principle described in example 2. Peptides are elongated with amino acid residues naturally encoded within the full length source allergen sequence using either isoform sequence Cry j 1.0101 (SEQ ID NO: 1) or isoform Cry j 2.0101 (SEQ ID NO: 2), isoform Cha o 1.0101 (SEQ ID NO: 3), or isoform Cha o 2.0101 (SEQ ID NO: 4) as templates .

By way of example the Cry j 1 peptide SEQ ID NO: 56 comprises the 16 amino acid sequence GNVLINESFGVEPVHP, which is C1 of formula I, and wherein A, B, a, b of formula I are null. No substitutions are introduced in C1, A1, or B1 of formula I.

Variant SEQ ID NO: 154 having the sequence GNVLINESFGVEPVHPQDGD, thus defined from C1 of Formula I and further elongated on the C-terminal side with 4 additional amino acid residues; i.e.

B1 of formula I being four residues. The four amino acid residues are identical to the amino acid residues found in the same position when sequence aligning to isoform Cry j 1.0101 (SED ID NO: 1). B, a, and b of formula I are null, and no substitution have been introduced in C, A1, or B1 .

- 5 I a similar manner it can easily be realised that variant SEQ ID NO: 157 illustrates an example defined from peptide SED ID NO: 56 (e.g. C1 is SEQ ID NO: 56). A1 and B1 of formula I are null but the sequence has been elongated with two and one non-coding amino acid residue (here arginine) in the N-terminal and C-terminal end of the C1 respectively.

Table A:

Allergen	SEQ ID NO:	Parent peptide	Start pos.	Peptide and Variant Sequence and Length
Cry j 1	48	*	89	LWIIIFSGNMNIKLKMP 16
Cry j 1	148			RDRPLWIIIFSGNMNIKLKMP 20
Cry j 1	149			RRDRPLWIIIFSGNMNIKLKMPR 22
Cry j 1	49	*	96	MNIKLKMPMYIAGYKT 16
Cha o 1	17		92	IFSKNLNLIKLNMPLYIAGNK 20
Cha o 1	150			RRIFSKNLNLIKLNMPLYIAGNKR 23
Cry j 1	151			MNIKLKMPMYIAGYKT <u>FDGR</u> 20
Cry j 1	152			RRMNIKLKMPMYIAGYKT <u>FDGR</u> R 23
Cry j 1	51	*	113	FDGRGAQVYIGNGGPC 16
Cry j 1	153			FDGRGAQVYIGNGGP <u>SVFIKR</u> 21
Cry j 1	53	*	129	VFIKRVSNIHGLYL 16
Cry j 1	56	*		GNVLINESFGVEPVHP 16
Cry j 1	154			GNVLINESFGVEPVHP <u>QDGD</u> 20
Cry j 1	155			GNVLINESFGVEPVHP <u>QD</u> 18
Cry j 1	156			DEGNVLINESFGVEPVHP <u>QDD</u> 21
Cry j 1	157			RRGNVLINESFGVEPVHPR 19
Cry j 1	59	*	177	RTATNIWIDHNSFSNS 16
Cry j 1	5		172	DALTTLRTATNIWIDHNSFSN 20
Cry j 1	158			DDALTTLRTATNIWIDHNSFSNDD 23
Cry j 1	159			RRDALTTLRTATNIWIDHNSFSNR 23
Cry j 1	160			RTATNIWIDHNSFSNS <u>SDGLVD</u> 22
Cry j 1	161			DRTATNIWIDHNSFSNS <u>SDGLVDD</u> 24
Cry j 1	64	*	215	HKVMLLGHDDAYSDDK 16
Cry j 1	63	*	209	SNNLFFNHHKVMLLGH 16
Cry j 1	162			SNNLFFNHHKVMLLGH <u>DDAYSDD</u> 23
Cha o 1	18		212	HFFNHHKVMLLGHSDIYSDD 20
Cha o 1	163			HFFNHHKVMLLGHSDIYSDD <u>K</u> 21
Cha o 1	164			DDHFFNHHKVMLLGHSDIYSDD <u>K</u> 23
Cha o 1	165			RHFFNHHKVMLLGHSDIYSDD <u>KR</u> 23
Cry j 1	66	*	233	SMKVTVAFNQFGPNCG 16
Cry j 1	6		232	KSMKVTVAFNQFGPNCGQRM 20

Allergen	SEQ ID NO:	Parent peptide	Start pos.	Peptide and Variant Sequence and Length
Cry j 1	166			KSMKVTVAFNQFGPNSGQRM 20
Cry j 1	167			DDKSMKVTVAFNQFGPNSGQRM ^{PR} 24
Cry j 1	168			SMKVTVAFNQFGPNSG 16
Cry j 1	169			DKSMKVTVAFNQFGPNSGQ ^R 20
Cry j 1	170			KSMKVTVAFNQFGPNSGQ ^R 19
Cry j 1	171			DDKSMKVTVAFNQFGPNSGQ ^R 21
Cry j 1	68	*	249	QRM ^{PR} ARYGLVHVANN 16
Cry j 1	172			GQRM ^{PR} ARYGLVHVANN 17
Cry j 1	173			RQRM ^{PR} ARYGLVHVANN ^R 18
Cry j 1	7		252	PRARYGLVHVANN ^{NYDPWT} I 20
Cry j 1	72	*	281	TILSEGN ^{SFTAPNES} Y 16
Cry j 1	174			PTILSEGN ^{SFTAPNESYKKQ} 20
Cry j 1	76	*	313	SNWVWQSTQDVFYNGA 16
Cry j 1	77	*		QDVFYNGAYFVSSGKY 16
Cry j 1	175			TQDVFYNGAYFVSSGKY ^E 18
Cry j 1	176			DDQDVFYNGAYFVSSGKY ^{ED} 20
Cry j 1	177			RRQDVFYNGAYFVSSGKY ^{ER} 20
Cry j 1	9		322	DVFYNGAYFVSSGKYEGGNI 20
Cry j 1	178			DVFYNGAYFVSSGKYEGGNI ^{YTKKE} 25
Cry j 1	81	*	353	GNATPQLTKNAGVLT ^C 16
Cry j 1	179			GNATPQLTKNAGVLT ^{SSL} SKR 21
Cry j 1	82	*	359	LTKNAGVLTCSLSK ^R C 16
Cry j 1	180			LTKNAGVLTSSLSK ^R S 16
Cry j 1	181			ATPQLTKNAGVLTSSLSK ^R S 20
Cry j 2	92	*	73	DCTEAFSTAWQAACKN 16
Cry j 2	182			DSTEAFSTAWQAASKN 16
Cry j 2	183			KHDSTEAFSTAWQAASKN 18
Cry j 2	95	*	97	GSKKFVNNLFFNGPC 16
Cry j 2	97	*	113	QPHFTFKVDGIIAAYQ 16
Cry j 2	184			RRQPHFTFKVDGIIAAYQ ^R 19
Cry j 2	98	*	122	DGIIAAYQNPASWKNN 16
Cry j 2	10		120	VDGIIAAYQNPASWK 15
Cry j 2	185			KVDGIIAAYQNPASWKNN ^R 19
Cry j 2	186			RKVDGIIAAYQNPASWKNN ^{RR} 21
Cry j 2	187			RRVDGIIAAYQNPASWK ^R 18
Cry j 2	188			TFKVDGIIAAYQNPASWKNN ^R 20
Cry j 2	100	*	137	RIWLQFAKLTGFTLMG 16
Cry j 2	25		135	NNRIWLQFAKLTGFT 15
Cry j 2	189			KNNRIWLQFAKLTGFT 16
Cry j 2	190			RKNNRIWLQFAKLTGFT ^{RR} 19
Cry j 2	26		185	AIKFDFSTGLIIQGL 15
Cry j 2	191			RDRPTAIKFDFSTGLIIQGL ^K 21
Cry j 2	192			RRDRPTAIKFDFSTGLIIQGL ^{KR} 23
Cry j 2	106	*	185	AIKFDFSTGLIIQGLK 16

Allergen	SEQ ID NO:	Parent peptide	Start pos.	Peptide and Variant Sequence and Length
Cry j 2	193			<u>RDRPTA</u> IKFDFSTGLIIQGLK 21
Cry j 2	107	*	193	GLIIQGLKLMNSPEFH 16
Cry j 2	11		195	IIQGLKLMNSPEFHL 15
Cry j 2	194			RRIIQGLKLMNSPEFHLR 18
Cry j 2	195			RRGLIIQGLKLMNSPEFHR 19
Cry j 2	196			<u>KFDFST</u> GLIIQGLKLMNSPEFH 22
Cry j 2	197			<u>RRKFDFST</u> GLIIQGLKLMNSPEFHR 25
Cry j 2	119	*	189	NSRAEVS ^Y VHVNGAKF 16
Cry j 2	198			<u>RENSRAEVS</u> ^Y VHVNGAKFIDT 21
Cry j 2	112	*	233	TDGIDIFASKNFHLQK 16
Cry j 2	27		235	GIDIFASKNFHLQKN 15
Cry j 2	199			<u>PNTD</u> GIDIFASKNFHLQKN 19
Cry j 2	200			<u>RDSPNTD</u> GIDIFASKNFHLQKN 22
Cry j 2	201			<u>RRDSPNTD</u> GIDIFASKNFHLQKNR 24
Cry j 2	113	*	241	SKNFHLQKNTIGTGDD 16
Cry j 2	202			<u>DIFASKNFHLQKNTIGTGDD</u> 20
Cry j 2	13		290	SRAEVS ^Y VHVNGAKF 15
Cry j 2	203		286	<u>RENSRAEVS</u> ^Y VHVNGAKFID 20
Cry j 2	204		285	<u>RRENSRAEVS</u> ^Y VHVNGAKFIDR 22
Cry j 2	12		240	ASKNFHLQKNTIGTG 15
Cry j 2	205			ASKNFHLQKNTIGTGDD 17
Cry j 2	206			RASKNFHLQKNTIGTGDDR 19
Cry j 2	125	*	337	ENPILINQFYCTSA 16
Cry j 2	214			ENPILINQFYSTSASA 16
Cry j 2	208			DENPILINQFYSTSASADD 19
Cry j 2	207			RRENPIILINQFYSTSASAR 19
Cry j 2	129	*	369	NIRGTSATAAAIQLKC 16
Cry j 2	209			<u>KNIRGTSATAAAIQLKSSDS</u> 20
Cry j 2	133	*	401	KLTSGKIASCLNDNAN 16
Cry j 2	211			KLTSGKIASLNDNAN 20
Cry j 2	210			<u>DISL</u> KLTSGKIASLNDNAN 20
Cry j 2	14		390	CKDIKLS ^D ISLKLTS 15
Cry j 2	212			SKDIKLS ^D ISLKLTS 15
Cry j 2	213			SKDIKLS ^D ISLKLTS ^{GK} 17

The present invention therefore provides in a first aspect, a composition comprising three peptides, which independently are 13 to 25 amino acid residues in length, wherein a first peptide is selected from group a) comprising peptides of either formula I or I*, a second peptide is selected from group b) comprising peptides of either formula II or II* and a third peptide is selected from group c) comprising peptides of group a) and b), wherein

- a peptide of formula I has an amino acid sequence defined by: a-A1-C1-B1-b

- a peptide of formula I* has an amino acid sequence defined by: a-A1-C1*-B1-b
- a peptide of formula II has an amino acid sequence defined by: a-A2-C2-B2-b
- a peptide of formula II* has an amino acid sequence defined by: a-A2-C2*-B2-b

5 and wherein

- C1 is an amino acid sequence selected from any one of SEQ ID NOs: 77, 48, 56 and 66,
- C1* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C1 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C1* is shorter than C1;
- 10 - C2 is an amino acid sequence selected from any one of SEQ ID NOs: 97, 107 and 125;
- C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C2* is shorter than C2;
- A1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- 15 - B1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- A2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- 20 - B2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

25 and wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

In an embodiment disclosed herein, the only substitution(s) in C1*, C2*, A1, A2, B1 and B2 is cysteine substituted with serine.

30 In one embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or SEQ ID NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions, and

35 a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,
C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,

- 5 wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

- 10 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or SEQ ID NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions.

In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

- 15 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 48 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48 or 77 of the same length, or SEQ ID NOs: 48 or 77 with 1 or 2 amino acid substitutions.

- 20 In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions.

- 25 In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

- 30 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48 and 56,
C1* in formula I* is either a fragment of SEQ ID NOs: 48 or 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48 or 56 of the same length, or SEQ ID NOs: 48 or 77 with 1 or 2 amino acid substitutions.

In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

- 5 C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions.

In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

- 10 C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions.

In a further embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

- 15 C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions.

- 20 In a further embodiment disclosed herein, a first peptide as defined herein is of formula I, that is to say that in any one of the above mentioned embodiments, a first peptide is of formula I, wherein C1, C1*, A1, B1, a, and b, are defined as above, meaning that a first peptide does not include any substitutions of C1.

In a further embodiment disclosed herein, a composition comprises a second peptide selected from peptides of formula II and II*, wherein

- 25 C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions.

- 30 In a further embodiment disclosed herein, a composition comprises a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97 and 107,
C2* in formula II* is either a fragment of SEQ ID NOs: 97 or 107 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NOs: 97 or 107 of the same length, or SEQ ID NOs:
97 or 107 with 1 or 2 amino acid substitutions.

- 5 In a further embodiment disclosed herein, a composition comprises a second peptide selected from
peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97 and 125,
C2* in formula II* is either a fragment of SEQ ID NOs: 97 or 125 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NOs: 97 or 125 of the same length, or SEQ ID NOs:
10 97 or 125 with 1 or 2 amino acid substitutions.

In a further embodiment disclosed herein, a composition comprises a second peptide selected from
peptides of formula II and II*, wherein

- C2 in formula II is an amino acid sequence of SEQ ID NO: 97,
C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions
15 compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino
acid substitutions.

In a further embodiment disclosed herein, a composition comprises a second peptide selected from
peptides of formula II and II*, wherein

- C2 in formula II is an amino acid sequence of SEQ ID NO: 107,
20 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions
compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino
acid substitutions.

In a further embodiment disclosed herein, a composition comprises a second peptide selected from
peptides of formula II and II*, wherein

- 25 C2 in formula II is an amino acid sequence of SEQ ID NO: 125,
C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions
compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino
acid substitutions.

- 30 In a further embodiment disclosed herein, a composition comprises a second peptide having
formula II, thus meaning that in any one of the above mentioned embodiments, a second peptide is
of formula II.

In a further embodiment disclosed herein, a composition comprises a third peptide selected from peptides of formula I, II, I* and II*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid

5 substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or

SEQ ID NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions,

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID

10 NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

In a further embodiment disclosed herein, a composition comprises a third peptide selected from peptides of formula I, II, I* and II*, wherein

15 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 48 or 77 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 48 or 77 of the same length, or

SEQ ID NOs: 48 or 77 with 1 or 2 amino acid substitutions,

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

20 C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID

NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

25 In an embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino

30 acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

5 a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

10 wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide. Exemplary peptide mixes is number 242 comprising peptides with SEQ ID NOs: 48, 97 and 125 or mixes comprising a variant of one or more of the SEQ ID NOs: 48, 97 and 125, for example peptide mix 242a comprising peptides with SEQ ID NOs: 148, 184 and 208. Further corresponding peptide mixes may be
15 provided by selecting another variant of SEQ ID NOs: 48, 97 and 125, for example those shown in Table A, herein.

In an embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

20 C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

25 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

30 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide. Exemplary peptide mixes is number 243 comprising peptides with SEQ ID NOs: 48, 97 and 107 or mixes comprising a variant of one or more of the SEQ ID NOs: 48, 97 and 107, for example peptide mixes 243a and 243b.

5 Further corresponding peptide mixes may be provided by selecting another variant of SEQ ID NOs: 48, 97 and 107, for example those shown in Table A, herein.

In an embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

10 C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

15 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

20 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide. Exemplary peptide mixes is

25 number 273 comprising peptides with SEQ ID NOs: 77, 97 and 107 or mixes comprising a variant of one or more of the SEQ ID NOs: 77, 97 and 107, for example peptide mixes 273a and 273b. Further corresponding peptide mixes may be provided by selecting another variant of SEQ ID NOs: 77, 97 and 107, for example those shown in Table A, herein.

30 In an embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 5 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

- 10 C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide. Exemplary peptide mixes is

- 15 number 240 comprising peptides with SEQ ID NOs: 77, 97 and 125 or mixes comprising a variant of one or more of the SEQ ID NOs: 77, 97 and 125, for example peptide mix 242a. Further corresponding peptide mixes may be provided by selecting another variant of SEQ ID NOs: 77, 97 and 125, for example those shown in Table A, herein

Examples of compositions comprising three peptides are peptide mixes numbered 242, 242a, 243, 20 243a, 243b, 273, 273a, 273b, 240, 240a, 246, 246a, 246b, 236, 236a, 236b, 238, 238a, 238b, 238c, 238d, 241, 241a, 241b, 245 and 244, wherein the individual peptides of the mix appears from Table 7a. As mentioned above, further corresponding combinations may be provided by selecting another variant of individual peptides, for example a variant disclosed in Table A.

- 25 In another embodiment disclosed herein, a composition comprising a first, second and third peptide may also comprise a fourth, fifth, sixth and/or further peptide independently selected from peptides of formula I, II, I* and II*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 49, 56, 59, 64, 66 and 77,

- 30 C1* in formula I* is either a fragment of SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 of the same length, or SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 with 1 or 2 amino acid substitutions,

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 98, 100, 107, 113 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 98, 100, 107, 113 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 98, 100, 107, 113 or 125 of the same length, or SEQ ID NOs: 97, 98, 100, 107, 113 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

In another embodiment disclosed herein, a composition comprising a first, second and third peptide may also comprise a fourth, fifth, sixth and/or further peptide independently selected from peptides of formula I, II, I* and II*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56, 66 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56, 66 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56, 66 or 77 of the same length, or SEQ ID NOs: 48, 56, 66 or 77 with 1 or 2 amino acid substitutions,

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107, and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107, or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107, or 125 of the same length, or SEQ ID NOs: 97, 107, or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

Examples of compositions comprising four peptides may be mixes numbered 253, 253a, 253b, 247, 247a, 247b, 293, 293a, 293b, 293c, 293d, 251, 251a, 251b, 248, 248a, 248b, 248c, 248d, 252, 252a, 252b, 252c, 252d, 254, 250, 255 and 249 shown in Table 8a, wherein the individual peptides of the mix appears from Table 8a. As mentioned above, further corresponding combinations may be provided by selecting another variant of individual peptides, for example a variant disclosed in Table A.

In another embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

a fourth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions; and

a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition. For example, a composition comprises the peptides as defined in mixes 153, 153a, and 153b.

In another embodiment disclosed herein, a composition comprises first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

- 5 a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

- 10 a fourth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions; and

- 15 a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 66,

C1* in formula I* is either a fragment of SEQ ID NO: 66 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 66 of the same length, or SEQ ID NO: 66 with 1 or 2 amino acid substitutions,

- 20 wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition. For example, the composition comprises the peptides as defined for mixes 256, 256a or 256b in Table 9a.

In another embodiment disclosed herein, a composition comprises a first peptide selected from peptides of formula I and I*, wherein

- 25 C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

- 30 C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

- 5 C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

a fourth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

- 10 C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions; and

a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

- 15 C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition. For example,
20 the composition comprises the peptides as defined for mixes 261, 261a or 261b, 261c, 261d in Table 9a.

Examples of compositions comprising five peptides as defined in any one of the peptide mixes numbered 153, 153a, 153b, 256, 256a, 256b, 259, 259a, 259b, 259c, 259d, 261, 261a, 261b, 261c and 261d is shown in Table 9a.

25

In an embodiment disclosed herein, a composition comprising a first, second, third, fourth, fifth peptide may also comprise a sixth peptide selected from peptides of formula I or formula I*, wherein C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 77 and 66,

- 30 C1* in formula I* is either a fragment of SEQ ID NOs: 77 or 66 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 77 or 66 of the same length, or SEQ ID NOs: 77 or 66 with 1 or 2 amino acid substitutions. For example, the composition comprises the peptides as defined for mixes 264, 264a, 264b, 264c, 264d, 265, 265a, 265b, 265c, 265d of Table 10a.

In an embodiment disclosed herein, a composition comprising a first, second, third, fourth, fifth peptide may also comprise a sixth peptide selected from peptides of formula I or formula I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 77 and 56,

- 5 C1* in formula I* is either a fragment of SEQ ID NOs: 77 or 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 77 or 56 of the same length, or SEQ ID NOs: 77 or 56 with 1 or 2 amino acid substitutions. For example, the composition comprises the peptides as defined for mixes 262 262a, 262b, 262c, 262d, 262, 262a, 262b of Table 10a.

- 10 In an embodiment disclosed herein, a composition comprising a first, second, third, fourth, fifth peptide may also comprise a sixth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions.

- 15 Examples of compositions comprising six peptides are peptide mixes numbered 263, 263a, 263b, 267, 267a, 267b, 267c, 267d, 264, 264a, 264b, 264c, 264d, 265, 265a, 265b, 265c, 265d, 262, 262a, 262b, 262c and 262d in Table 10a, wherein the individual peptides of the mixes also appears.

- 20 In an embodiment disclosed herein, a composition comprises a first peptide having the amino acid sequence of:

- a) SEQ ID NO: 48 or SEQ ID NO:148,
- b) SEQ ID NO: 56 or SEQ ID NOs: 154, 155, 156 or 157,
- c) SEQ ID NO: 66 or SEQ ID NOs: 170, 166, 167 or 6, or
- d) SEQ ID NO: 77 or SEQ ID NO: 176.

- 25 In an embodiment disclosed herein, a composition comprises a first peptide may also comprise a second peptide having the amino acid sequence of:

- e) SEQ ID NO: 97 or SEQ ID NO:184,
- f) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195, or
- g) SEQ ID NO: 125 or SEQ ID NO: 208.

In an embodiment disclosed herein, a composition comprises a first peptide as defined above in a) to d) and a second peptide as defined above in e) to g) may also comprise a third peptide, a fourth peptide, a fifth peptide and/or a sixth peptide each having an amino acid sequence as a peptide defined in a) to g) above, and not selected from the same a) to g) as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprises three peptides, which independently are 13 to 25 amino acid residues in length, said composition comprising:

a first peptide having the amino acid sequence of:

a) SEQ ID NO: 48 or SEQ ID NO:148,

10 b) SEQ ID NO: 56 or SEQ ID NOs: 154, 155, 156 or 157,

c) SEQ ID NO: 66 or SEQ ID NOs: 170, 166, 167 or 6,

d) SEQ ID NO: 77 or SEQ ID NOs: 176;

a second peptide having the amino acid sequence of:

e) SEQ ID NO: 97 or SEQ ID NO:184,

15 f) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195,

g) SEQ ID NO: 125 or SEQ ID NOs: 208; and

a third peptide having the same amino acid sequence as a peptide defined in a) to g), and not selected from the same a) to g) as any other peptide in the composition.

20 In an embodiment disclosed herein, a composition comprises a first peptide having the amino acid sequence of:

h) SEQ ID NO: 48 or SEQ ID NO:148,

i) SEQ ID NO: 77 or SEQ ID NO: 176; and/or

a second peptide having the amino acid sequence of:

j) SEQ ID NO: 97 or SEQ ID NO:184,

25 k) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195,

l) SEQ ID NO: 125 or SEQ ID NOs: 208; and/or

a third peptide having the same amino acid sequence as a peptide defined in h) to l), and not selected from the same h) to l) as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprises a first peptide having the amino acid sequence of:

- 5 m) SEQ ID NO:148,
 n) SEQ ID NOs: 155 or 157,
 o) SEQ ID NOs: 170 or 167, or
 p) SEQ ID NO: 176; and/or

the second peptide having the amino acid sequence of:

- 10 q) SEQ ID NO:184,
 r) SEQ ID NOs: 194 or 195, or
 s) SEQ ID NO: 208; and/or

the third peptide having the same amino acid sequence as a peptide defined above in m) to s), and not selected from the same m) to s) as any other peptide in the composition.

- 15 In an embodiment disclosed herein, a composition comprises a first peptide having the amino acid sequence of:

- t) SEQ ID NO:148,
 u) SEQ ID NO: 176; and/or

a second peptide having the amino acid sequence of:

- 20 v) SEQ ID NO:184,
 w) SEQ ID NOs: 194 or 195,
 x) SEQ ID NO: 208; and/or

a third peptide having the same amino acid sequence as a peptide defined in t) to x), and not selected from the same t) to x) as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprising a first, second and third peptide may also comprise a fourth, fifth or sixth peptide independently having the same amino acid sequence as a peptide selected from a) to g) as defined above, each not from the same a) to g) as any other peptide in the composition.

- 5 In an embodiment disclosed herein, a composition comprising a first, second and third peptide may also comprise a fourth, fifth or sixth peptide independently having the same amino acid sequence as a peptide selected from h) to l) as defined above, each not from the same h) to n) as any other peptide in the composition.

- 10 In an embodiment disclosed herein, a composition comprising a first, second, third, fourth, fifth or sixth peptide may also comprise a further peptide independently having the same amino acid sequence as a peptide selected from a) to l) as defined above, each not from the same a) to g) or h) to l) as any other peptide in the composition.

- 15 In an embodiment disclosed herein, a composition comprises a first, second and third peptide may also comprise a fourth, fifth, sixth and/or further peptide, which peptide(s) independently are 13 to 25 amino acid residues in length, wherein any one of the fourth, fifth, sixth or further peptide is of either formula III or III* or formula IV or IV*, wherein

- 20 - a peptide of formula III has an amino acid sequence defined by: a-A3-C3-B3-b
 - a peptide of formula III* has an amino acid sequence defined by: a-A3-C3*-B3-b
 - a peptide of formula IV has an amino acid sequence defined by: a-A4-C4-B4-b
 - a peptide of formula IV* has an amino acid sequence defined by: a-A4-C4*-B4-b

and wherein

- 25 - C3 is an amino acid sequence selected from any one of SEQ ID NOs: 49, 59, or 64,
 - C3*consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C3 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C3* is shorter than C3;
 - C4 is an amino acid sequence selected from any one of SEQ ID NOs: 14, 98, 100 or 113,
 - C4*consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C4 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C4* is shorter than C4;
 30 - A3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
 - B3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
 35 - A4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;

- B4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

5 and wherein C3, C3*, C4, or C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO as C1, C1*, C2, C2*, C3 or C3* or C4 or C4* as any other peptide in the composition.

10 Examples of peptides of formula III* and IV* may be found in Table A by looking up peptides that are variants of peptides with SEQ ID NOs: 49, 59, 64, 14, 98, 100 and 113 in Table A.

In a further embodiment, the only substitution(s) in C3*, C4*, A3, A4, B3 and B4 is cysteine substituted with serine.

In an embodiment disclosed herein, a composition comprises a fourth, fifth, sixth and/or further peptide selected from peptides of formula III, III*, IV and IV*,

15 wherein C3 in formula III is an amino acid sequence of SEQ ID NO: 49,

C3* in formula III* is either a fragment of SEQ ID NO: 49 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 49 of the same length, or SEQ ID NO: 49 with 1 or 2 amino acid substitutions;

20 wherein C4 in formula IV is an amino acid sequence selected from any one of SEQ ID NOs: 98 and 100, C4* in formula IV* is either a fragment of SEQ ID NOs: 98 or 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 98 or 100 of the same length, or SEQ ID NOs: 98 or 100 with 1 or 2 amino acid substitutions.

25 In an embodiment such a fourth, fifth, sixth and/or further peptide selected from peptides of formula III, III*, IV and IV* may be in a composition with a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions,

30 a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77,

- 5 C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions, and peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

- 10 C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions.

In one embodiment disclosed herein, a composition comprises the peptides as defined for mixes numbered 282, 277, 281, 297, 301, 302, 295, 299, 313, 316, 320, 315, 335, 336, 340, 335a, 335b, 335c, 335d, 335e, 335f of Table 11a

- 15 In a further embodiment disclosed herein, a composition comprises

a first peptide of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

- 20 C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 25 C2* in formula II* is of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

- 30 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions,

a fourth peptide selected from peptides of formula IV and IV*, wherein

C4 in formula IV is an amino acid sequence of SEQ ID NO: 100, C4* in formula IV* is either a fragment of SEQ ID NO: 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 100 of the same length, or SEQ ID NO: 100 with 1 or 2 amino acid substitutions, and

5 a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

10 wherein C1, C1*, C2, C2*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C4 as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprises five peptides as defined in any one of the peptide mixes numbered 313, 313a, 313b and 313c as shown in Table 11a.

In a further embodiment disclosed herein, a composition comprises

15 a first peptide of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

20 a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions,

25 a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions,

a fourth peptide selected from peptides of formula IV and IV*, wherein

wherein C4 in formula IV is an amino acid sequence of SEQ ID NO: 100, C4* in formula IV* is either a fragment of SEQ ID NO: 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 100 of the same length, or SEQ ID NO: 100 with 1 or 2 amino acid substitutions, and

a fifth peptide selected from peptides of formula III and III*, wherein

wherein C3 in formula III is an amino acid sequence of SEQ ID NO: 49, C3* in formula III* is either a fragment of SEQ ID NO: 49 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 49 of the same length, or SEQ ID NO: 49 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, C2*, C3, C3*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C3, C4 as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprises the peptides as defined in mix 315.

In an embodiment disclosed herein, a composition comprises five peptides as defined in any one of the peptide mixes numbered 315, 315a, 315b, 315c, 315d, 315e and 315f as shown in Table 11a.

In an embodiment disclosed herein, a composition comprising a first, second, third, fourth and fifth peptide may also comprise a sixth peptide selected from peptides of formula IV and IV*,

wherein C4 in formula IV is an amino acid sequence of SEQ ID NO: 98, C4* in formula IV* is either a fragment of SEQ ID NO: 98 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 98 of the same length, or SEQ ID NO: 98 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, C2*, C3, C3*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C3, C4 as any other peptide in the composition.

In an embodiment disclosed herein, a composition comprises the peptides as defined in mix 335 of Table 11a.

In an embodiment disclosed herein, a composition comprises six peptides as defined in any one of the peptide mixes numbered 335, 335a, 335b, 335c, 335d, 335e and 335f as shown in Table 11a.

In an embodiment disclosed herein, a composition comprises three or at least three peptides having the amino acid sequences as defined for peptide mixes numbered 242, 242a, 243, 243a,

243b, 273, 273a, 273b, 240, 240a, 246, 246a, 246b, 236, 236a, 236b, 238, 238a, 238b, 238c, 238d, 241, 241a, 241b, 245 and 244 as shown in Table 7a.

In an embodiment disclosed herein, a composition comprises four or at least four peptides having the amino acid sequences as defined for peptide mixes numbered 253, 253a, 253b, 247, 247a,
 5 247b, 293, 293a, 293b, 293c, 293d, 251, 251a, 251b, 248, 248a, 248b, 248c, 248d, 252, 252a, 252b, 252c, 252d, 254, 250, 255 and 249 as shown in Table 8a.

In an embodiment disclosed herein, a composition comprises five or at least five peptides having the amino acid sequences as defined for peptide mixes numbered 153, 153a, 153b, 256, 256a, 256b, 259, 259a, 259b, 259c, 259d, 261, 261a, 261b, 261c and 261d as shown in Table 9a.

10 In an embodiment disclosed herein, a composition comprises six or at least six peptides having the amino acid sequences as defined for peptide mixes numbered 263, 263a, 263b, 267, 267a, 267b, 267c, 267d, 264, 264a, 264b, 264c, 264d, 265, 265a, 265b, 265c, 265d, 262, 262a, 262b, 262c and 262d as shown in Table 10a.

In an embodiment disclosed herein, a composition comprises three, four, five or six peptides having
 15 the amino acid sequences as defined for peptide mixes numbered 282, 277, 281, 297, 301, 302, 295, 299, 316, 320, 313, 313a, 313b, 313c, 315, 315a, 315b, 315c, 315d, 315e, 315f, 335, 336, 340, 335a, 335b, 335c, 335d, 335e and 335f as shown in Table 11a.

In an embodiment disclosed herein, a composition comprises 4, 5, 6, 7 or 8 peptides or at least 4,
 20 5, 6, 7 or 8 peptides.

In an embodiment disclosed herein, a composition comprises at the most 4, 5, 6, 7 or 8 peptides.

In an embodiment disclosed herein, the C1, C1*, C2, or C2* in the third peptide binds at least one additional HLA Class II molecule than is bound by the C1 or C1* in the first peptide and the C2 or C2* bound in the second peptide.

25 In a further embodiment disclosed herein, a composition comprising a fourth, fifth, sixth and/or further peptide the C1, C1*, C2, C2*, C3, C3*, C4, or C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C3, C4 as any other peptide in the composition.

In a further embodiment disclosed herein, a composition comprising a fourth, fifth and/or sixth
 30 peptide the C1, C1*, C2, C2*, C3, C3*, C4, or C4* in each of the fourth, fifth or sixth peptide binds at least one additional HLA Class II molecule than is bound by the C1, C1*, C2, C2*, C3, C3*, C4, or C4* present in any one of the other peptides in the composition.

In a further embodiment disclosed herein, a composition comprising a fourth, fifth and/or sixth peptide selected from formula III, III*, IV or IV*, the C3, C3*, C4, or C4* in each of the fourth, fifth or sixth peptide binds at least one additional HLA Class II molecule than is bound by the C1, C1*, C2, or C2* present in any one of the other peptides in the composition.

- 5 In an embodiment disclosed herein, at least one of the amino acid substitutions in C1*, C2*, A1, B1, A2 and B2 is the substitution of a cysteine amino acid residue by a serine amino acid residue or by a 2-aminobutyric acid amino acid residue.

- In an embodiment disclosed herein, at least one of the amino acid substitutions in C3*, C4*, A3, B3, A4 and B4 is the substitution of a cysteine amino acid residue by a serine amino acid residue or
10 by a 2-aminobutyric acid amino acid residue.

In an embodiment disclosed herein, at least one of the amino acid substitutions in C1*, C2*, A1, B1, A2 and B2 is the substitution of a cysteine amino acid residue by a serine amino acid residue.

In an embodiment disclosed herein, at least one of the amino acid substitutions in C1*, C2*, A3, B3, A4 and B4 is the substitution of a cysteine amino acid residue by a serine amino acid residue.

- 15 In an embodiment disclosed herein, any cysteine amino acid residue in any of the peptides of the composition is substituted by a serine amino acid residue or by a 2-aminobutyric acid amino acid residue.

In a further embodiment disclosed herein, any cysteine amino acid residue in any of the peptides of the composition is substituted by a serine amino acid residue.

- 20 In an embodiment disclosed herein, the peptides of the composition in combination bind at least 18 of 26 HLA Class II molecules selected from the group consisting of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101,
25 DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101, DRB5_0101, such as at least 19, 20, 21, 22, 23, 24, 25 or 27 of said HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

- In an embodiment disclosed herein, the peptides of the composition in combination bind at least
30 70% of the HLA Class II molecules of Table 5, column 3, such as at least 75%, 80%, 84%, 88%, 90%, 92%, 94%, 96%, 98% of said group of HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

In an embodiment disclosed herein, any of the amino acid sequences of the C1* and C2* in the composition binds at least 70% of the HLA Class II molecules that C1 and C2 binds, respectively, such as binds at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that C1 and C2 binds, respectively, when binding is determined by similar in vitro or in silico test conditions.

In an embodiment disclosed herein, any of the amino acid sequence(s) of a peptide of formula I or I* binds at least 70% of the HLA Class II molecules that the respective C1 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C1 binds, when binding is determined by similar in vitro or in silico test conditions.

In an embodiment disclosed herein, the amino acid sequence of a peptide(s) of formula II or II* binds at least 70% of the HLA Class II molecules that the respective C2 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C2 binds, when binding is determined by similar in vitro or in silico test conditions.

In an embodiment disclosed herein, the amino acid sequence of a peptide(s) of formula III or III* binds at least 70% of the HLA Class II molecules that the respective C3 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C3 binds, when binding is determined by similar in vitro or in silico test conditions.

In an embodiment disclosed herein, the amino acid sequence of a peptide(s) of formula IV or IV* binds at least 70% of the HLA Class II molecules that the respective C4 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C4 binds, when binding is determined by similar in vitro or in silico test conditions.

In an embodiment disclosed herein, the group of HLA Class II molecules consists of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101 and DRB5_0101.

In an embodiment disclosed herein, the group of HLA Class II molecules consists of the HLA Class II molecules shown in Table 5 column 2 or 3.

In an embodiment disclosed herein, any peptide of the composition elicits, stimulates or induces an in vitro T cell proliferation response or an in vitro IL-5 cytokine response of T cells or PBMC's obtained from an individual allergic or sensitized to cedar pollen.

In an embodiment disclosed herein, any peptide of the composition elicits, stimulates or induces an in vitro T cell proliferation response or an in vitro IL-5 cytokine response of T cells or PBMC's obtained from an individual allergic or sensitized to a cedar pollen allergen selected from Cry j 1 and Cry j 2.

- 5 In an embodiment disclosed herein, the 13 to 16 contiguous amino acid residues of the C1* and C2* are independently selected from 14 to 16 contiguous amino acid residues of the C1* and C2*, 15 to 16 contiguous amino acid residues of the C1* and C2* and 16 contiguous amino acid residues of the C1* and C2*.

- 10 In an embodiment disclosed herein, the 13 to 16 contiguous amino acid residues of the C3* and C4* are independently selected from 14 to 16 contiguous amino acid residues of the C3* and C4*, 15 to 16 contiguous amino acid residues of the C3* and C4* and 16 contiguous amino acid residues of the C1* and C2*.

- 15 In an embodiment disclosed herein, the 0-6 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4 are independently selected from 0-5 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively, such as 0-4 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively, such as 0-3 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively, such as 0-2 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively, such as 0-1 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively, such as 0 contiguous amino acid residues of A1, A2, A3, A4, B1, B2, B3 and B4, respectively.
- 20 A1, A2, A3, A4, B1, B2, B3 and B4, respectively.

In an embodiment disclosed herein, the number of amino acid residue substitutions of the C1*, C2*, C3* and C4* are independently selected from 0, 1 or 2.

In an embodiment disclosed herein, the number of amino acid residue substitutions of the A1, A2, A3, A4, B1, B2, B3 and B4 are independently selected from 0 or 1.

- 25 In an embodiment disclosed herein, the total number of amino acid residues in the A1 and B1 of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

- 30 In an embodiment disclosed herein, the total number of amino acid residues in A2 and B2 of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

In an embodiment disclosed herein, the total number of amino acid residues in A3 and B3 of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

In an embodiment disclosed herein, the total number of amino acid residues in A4 and B4 of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

5 In an embodiment disclosed herein, the total number of amino acid residues in the a, A1, B1 and b of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

In an embodiment disclosed herein, the total number of amino acid residues in the a, A2, B2 and b of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

10 In an embodiment disclosed herein, the total number of amino acid residues in the a, A3, B3 and b of formulas III and III* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

In an embodiment disclosed herein, the total number of amino acid residues in the a, A4, B4 and b of formulas IV and V* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed
15 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

In an embodiment disclosed herein, the amino acid residues of a and b of formulas I, II* II, II* III, III* IV, IV* in each formula independently is 0, 1 or 2 lysine (K).

In an embodiment disclosed herein, the amino acid residues of a and b of formulas I, II* II, II* III, III* IV, IV* in each formula independently is 0, 1 or 2 arginine (R).

20 In an embodiment disclosed herein, the amino acid residues of a and b of formulas I, II* II, II* III, III* IV, IV* in each formula independently is 0, 1 or 2 aspartic acid (D).

In an embodiment disclosed herein, the amino acid residues of a and b of formulas I, II* II, II* III, III* IV, IV* in total in each formula is 0, 1, 2 or 3 amino residues.

25 In an embodiment disclosed herein, the length of the peptides each is independently selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25 amino acid residues in length.

Variants

As mentioned, a number of modifications including substitutions can be made to each peptide, such as parent peptides.

When referring herein to a "variant" or "variants" of (parent) peptides, or when referring to "a derivative" or "derivatives" of (parent) peptides, or when referring to "a salt" or "salts" of a (parent) peptide, the following considerations apply:

5 The term "parent peptide" as used herein denotes an individually identified peptide, with a region containing at least one T cell epitope that herein is found to elicit an *in-vitro* T cell response in a high fraction of the donor population and to have broad HLA Class II coverage. For example, the individual peptides having an amino acid sequence shown in Table A and indicated with an asterisk, are considered parent peptides. As shown herein, an individual peptide derived from the same region of the allergen as the parent peptide and which
10 overlaps with at least 11 contiguous amino acid residues of the parent peptide is expected to produce a T cell response in a high fraction of the same donors as the parent peptide. Such individual peptides are thus said to belong to the same peptide group of individual peptides as the parent peptide and are considered to be variants (or modifications) of the parent peptide.

15 A (parent) peptide described herein may be modified as described herein. Such peptides are referred to as variant peptides. Some modifications correspond to naturally occurring variations of the original allergens, such as in isoforms (within species or intra species) or in homologous allergens in other cedar species (inter species). Other modifications are non-natural modifications of the parent peptide.

20 A parent peptide described herein may contain one or more modifications, which optionally may result in greater or less activity or function, for example in the ability to elicit, stimulate or induce an in-vitro immune response (e.g. T cell proliferation or T cell cytokine production); in the ability to bind HLA Class II alleles; in the ability to induce or enhance immunological tolerance to a relevant antigen, e.g. allergen; or in the ability to dissolve in solvents e.g. in
25 an aqueous solution, or in the ability to resist oxidation.

A variant, which is also termed a "variant peptide" or "modified peptide" herein, is a peptide, which is derived from but not identical to a parent peptide. A variant may for instance include one or more deletions of amino acid residues from the N- and/or C- terminal end of the parent peptide, one or more additions of amino acid residues to the N- and/or C- terminal of
30 the parent peptide and/or one or more amino acid substitutions, additions or deletions within the amino acid sequence of the parent peptide. One type of variant is a "derivative", where chemical modifications are introduced, for instance in the side-chains of the amino acid residues of the parent peptide's amino acid sequence (thus effectively resulting in a peptide that includes an amino acid residue substitution relative to the parent peptide). A derivative

can also include a chemical modification that involves the N-terminal amino group and/or the C-terminal COOH group. Derivatives are described in more detail herein. It is important to note that some derivatives of the parent peptides described herein are those that could be obtained by substituting an amino acid residue with another naturally occurring amino acid residue, whereas other derivatives involve chemical modifications that result in the provision of peptides that could not be encoded by a nucleic acid sequence.

Typically, a longer variant of the parent peptide may be up to 25 amino acids in length, for example up to 24, 23, 22, 21, 20, 19, 18, 17, 16 amino acids in length. The longer variant may comprise the amino acid sequence of a parent peptide disclosed herein, or an amino acid sequence having at least 65% identity or similarity over the length of the amino acid sequence of the parent peptide or a fragment thereof, such as over at least 12 contiguous amino acids, for example over at least 13, 14, 15, 16, 17, 18, 19, 20 contiguous amino acids of the parent peptide. Typically, the longer variant comprises an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% or 99% identity or similarity over the length of the amino acid sequence of the parent peptide or over at least 12 contiguous amino acids, for example over at least 13, 14, 15, 16, 17, 18, 19 or 20 contiguous amino acids of the parent peptide. Therefore, in some embodiments, a variant of the parent peptide is a longer peptide up to 30 amino acid residues in length that comprises one or more additional amino acid residues at the N- and/or C- terminal end of the parent peptide or comprises an amino acid sequence having at least 80%, such as at least 85%, 90% or 95% identity or similarity over at least 14 contiguous amino acids of the parent peptide, such as over at least 15, 16, 17, 18 contiguous amino acids of the parent peptide.

A variant of the parent peptide may also include a fragment of a parent peptide disclosed herein. A fragment of the parent peptide can have one or more amino acids less than the parent peptide, either comprising deletions from within the amino acid sequence of the parent peptide and/or amino acid deletions from the N- and/or C- terminus of the parent peptide. Typically, a fragment will have a length of at least 13 amino acids, for example at least 14, 15, 16 or 17 amino acids, and will have at least 65% identity or similarity over the length of the fragment, or over the length of at least 12 contiguous amino acids of the parent peptide, when aligned with the parent peptide. In some embodiments, the percentage identity or similarity is at least 70%, 75%, 80%, 85%, 90% or 95% over the length of the fragment, or over at least 13, 14 or 15 contiguous amino acids of the parent peptide. Therefore, in some embodiments, a variant thereof may be a shorter peptide comprising an amino acid sequence having at least 80%, such as at least 85%, 90% or 95% identity or similarity over at least 14 contiguous amino acids of the parent peptide, such as over at least 15, 16, 17, 18 contiguous amino acids of the parent peptide.

As mentioned, a variant of a parent peptide may comprise additional amino acids or may consist of a fragment of the parent peptide. Thus, a variant of a parent peptide may consist of 13-25 amino acids, for example, 14-25, 15-25, 15-25, 13-24, 14-24, 15-24, 16-24, 3-22, 14-22, 15-22, 16-22, 13-20, 14-20, 15-20, 16-20 amino acids, such as particularly 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 amino acids.

Moreover, a variant of a parent peptide may comprise an amino acid sequence having at least 65% sequence identity or similarity over at least 14 contiguous amino acids of the parent peptide sequence, optionally wherein the percent sequence identity or similarity is at least 70% 80%, 85%, 90% or 95% over at least 15 contiguous amino acids of the parent peptide sequence, such as over at least 16 contiguous amino acids of the parent peptide sequence.

In still other particular embodiments, the variant is a peptide consisting of 15-25 amino acids and comprises an amino acid sequence having at least 80% identity or similarity over at least 11-13 or 14-15 contiguous amino acids of the parent sequence.

The term "identity" and "identical" and grammatical variations thereof, as used herein, mean that two or more referenced entities are the same (e.g., amino acid sequences). Thus, where two peptides are identical, they have the same amino acid sequence. The identity can be over a defined area, e.g. over at least 13, 14, 15 or 16 contiguous amino acids of the parent peptide sequence, optionally wherein the alignment is the best fit with gaps permitted.

For example, to determine whether a variant peptide has at least 80% similarity or identity over at least 13 contiguous amino acid residues of the parent peptide sequence, the variant peptide may be aligned with the parent peptide and the percent identity calculated with respect to the identical amino acid residues found within the amino acid sequence of the variant peptide that overlaps with the 13 contiguous amino acids of the parent peptide sequence.

Identity can be determined by comparing each position in aligned sequences. A degree of identity between amino acid sequences is a function of the number of identical or matching amino acids at positions shared by the sequences, i.e. over a specified region. Optimal alignment of sequences for comparisons of identity may be conducted using a variety of algorithms, as are known in the art, including the Clustal Omega program available at the URL: <http://www.ebi.ac.uk/Tools/msa/clustalo/>, the local homology algorithm of Smith and Waterman, 1981, *Adv. Appl. Math* 2: 482, the homology alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Natl. Acad. Sci. USA* 85: 2444, and the computerized implementations of

these algorithms (such as GAP, BESTFIT, FASTA and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, Madison, WI, U.S.A.). Sequence identity may also be determined using the BLAST algorithm, described in Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-10 (using the published default settings). Software for performing BLAST analysis may be available through the National Center for Biotechnology Information (through the internet at the URL, <http://www.ncbi.nlm.nih.gov/>). Such algorithms that calculate percent sequence identity (homology) generally account for sequence gaps and mismatches over the comparison region or area. For example, a BLAST (*e.g.*, BLAST 2.0) search algorithm (see, *e.g.*, Altschul *et al.*, *J. Mol. Biol.* 215:403 (1990), publicly available through NCBI) has exemplary search parameters as follows: Mismatch -2; gap open 5; gap extension 2. For polypeptide sequence comparisons, a BLASTP algorithm is typically used in combination with a scoring matrix, such as PAM100, PAM 250, BLOSUM 62 or BLOSUM 50. FASTA (*e.g.*, FASTA2 and FASTA3) and SSEARCH sequence comparison programs are also used to quantitate the extent of identity (Pearson *et al.*, *Proc. Natl. Acad. Sci. USA* 85:2444 (1988); Pearson, *Methods Mol Biol.* 132:185 (2000); and Smith *et al.*, *J. Mol. Biol.* 147:195 (1981). Programs for quantitating protein structural similarity using Delaunay-based topological mapping have also been developed (Bostick *et al.*, *Biochem Biophys Res Commun.* 304:320 (2003)).

The term "similarity" and "similar" and grammatical variations thereof, as used herein, mean that an amino acid sequence contains a limited number of conservative amino acid substitutions compared to a peptide reference sequence, *e.g.* the variant peptide versus the parent peptide. A variety of criteria can be used to indicate whether amino acids at a particular position in a peptide are similar. In making changes, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like, and such substitutions may be assayed for their effect on the function of the peptide by routine testing.

Substitutions may be conservative or non-conservative amino acid substitutions. A "conservative substitution" is the replacement of one amino acid by a biologically, chemically or structurally similar residue. Biological similarity means that the substitution does not destroy a biological activity, *e.g.* T cell reactivity or HLA coverage. Structural similarity means that the amino acids have side chains with similar length, such as alanine, glycine and serine, or a similar size. Chemical similarity means that the residues have the same charge, or are both either hydrophilic or hydrophobic. For example, a conservative amino acid substitution is one in which an amino acid residue is replaced with an amino acid residue having a similar side chain, for example amino acids with basic side chains (*e.g.*, lysine, arginine, histidine); acidic side chains (*e.g.*, aspartic acid, glutamic acid); uncharged polar side chains (*e.g.*,

glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, histidine); nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan); beta-branched side chains (e.g., threonine, valine, isoleucine), and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan). Particular examples include the substitution of one hydrophobic residue, such as isoleucine, valine, leucine or methionine, for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic acid for aspartic acid, or glutamine for asparagine, serine for threonine, and the like. Proline, which is considered more difficult to classify, shares properties with amino acids that have aliphatic side chains (e.g., Leu, Val, Ile, and Ala). In certain circumstances, substitution of glutamine for glutamic acid or asparagine for aspartic acid may be considered a similar substitution in that glutamine and asparagine are amide derivatives of glutamic acid and aspartic acid, respectively.

As mentioned, a variant of a parent peptide disclosed herein may comprise one or more additional amino acid residues at the N- and/or C- terminal end than the parent peptide. Such amino acid residues may be naturally occurring amino acids or non-naturally occurring amino acids. In some embodiments, the one or more additional amino acids are the same amino acid or amino acid sequence flanking the N- and/or C- terminal ends of the parent peptide when aligned with the amino acid sequence of the allergen isoform it is present in, based upon or derived from or is aligned with another isoform of the same allergen. Thus, additional amino acids may be the amino acids flanking the N- and/or C-terminal ends of the parent peptide when aligned to the respective antigen. Alternatively the parent peptide may be aligned to an sequence of a different species from the same allergen group when changing amino acids.

A variant peptide may include a number of variations compared to the parent peptide, for example to increase or decrease physical or chemical properties of the parent peptide, for example to decrease its ability to resist oxidation, to improve or increase solubility in aqueous solution, to decrease aggregation, to decrease synthesis problems, etc.

Accordingly, in some embodiments of the invention, a variant of a parent peptide comprises:

a) one or more (e.g. 1, 2, or 3) amino acid substitutions in the parent peptide sequence, for example a glutamate residue at the N-terminus of the parent peptide may be replaced with pyroglutamate and/or one or more cysteine residues in the parent peptide may be replaced with serine or 2-aminobutyric acid; and/or

b) one or more amino acid additions (e.g. 1, 2, 3, 5, 4, 6, 7, 8) to the parent peptide sequence, for example wherein the variant comprises one or more (e.g. 1, 2, 3, or 4) lysine residue(s) and/or one or more (e.g. 1, 2, 3, or 4) arginine residue(s) and/or one or more positively charged residues added at the N- and/or C-terminus of the parent peptide or to a fragment of the parent peptide consisting of at least 14 contiguous amino acids of the parent peptide (such as at least 15 contiguous amino acids); and/or

c) one or more amino acid deletions from the parent peptide, for example wherein a hydrophobic residue the up to three amino acids from the N- or C- terminus of the parent peptide are deleted; and/or any two consecutive amino acids comprising the sequence Asp-Gly up to four amino acids from the N- or C- terminus of the parent peptide are deleted.

Furthermore, in some embodiments, a variant of a parent peptide may comprise one, two, three or more lysine or arginine amino acid residue(s) added to the N- and/or C-terminus of the parent peptide that have been extended with one or more, e.g. 1, 2, 3, 4, or 5 amino acid residues, optionally of the wild type sequence the peptide is based upon or another wild type isoform.

As described above the phrase "a variant sequence, a derivative or a salt" of a peptide described herein is meant to encompass modifications of any such peptide, including variations in the amino acid sequence, derivatives of the peptides, derivatives of a variant sequence, and salts, including a salt of a peptide which itself is a variant sequence and/or a derivative. It should be understood that any peptide specifically disclosed in the present specification and claims may be replaced by a variant sequence, a derivative or a salt thereof, including a salt of a variant, a salt of a derivative, or a salt of a derivative of a variant.

The term "variant sequence" means that any peptide disclosed herein may be replaced by a variant sequence of the peptide, for example a variant sequence having the same functionality as the peptide from which it is modified (the "original" or "parent" peptide). The variant sequence may thus bind to the same or substantially the same HLA Class II alleles as the peptide from which it is modified. Thus, in some embodiments, the variant sequence binds to the same, substantially the same or at least 80%, such as at least 85%, 90% or 95% or more of the Class HLA II alleles binding to the peptide from which the variant sequence is modified, wherein optionally the Class HLA II alleles consist of the group of HLA-DPA1*02:01-DPB1*01:01, HLA-DPA1*01:03-DPB1*02:01, HLA-DPA1*01:03-DPB1*03:01, HLA-DPA1*01:03-DPB1*04:01, HLA-DPA1*01:03-DPB1*04:02, HLA-DPA1*02:02-DPB1*05:01, HLA-DPA1*02:01-DPB1*14:01, HLA-DQA1*05:01-DQB1*02:01, HLA-DQA1*05:01-DQB1*03:01, HLA-DQA1*03:01-DQB1*03:02, HLA-DQA1*04:01-DQB1*04:02,

HLA-DQA1*01:01-DQB1*05:01, HLA-DQA1*01:02-DQB1*06:02, HLA-DRB1*01:01, HLA-DRB1*03:01, HLA-DRB1*04:01, HLA-DRB1*04:05, HLA-DRB1*07:01, HLA-DRB1*09:01, HLA-DRB1*11:01, HLA-DRB1*12:01, HLA-DRB1*13:02, HLA-DRB1*15:01, HLA-DRB3*01:01, HLA-DRB3*02:02, HLA-DRB4*01:01 and HLA-DRB5*01:01.

- 5 A variant sequence may share the ability to recognize a T cell epitope with the peptide from which it is modified. A T cell epitope may be determined by *in vitro* T cell proliferation assays e.g. as described herein in Example 1.

10 A variant sequence may be a homologous peptide of the same length, a longer peptide or a shorter peptide (i.e. a fragment of the parent peptide), including variants comprising the same sequence as the parent peptide or that have at least partial sequence identity or homology with the parent peptide. The identity or homology can be over a defined area of the sequence, such as over at least 15, 16, 17, 18, 19 or 20 contiguous amino acids or over the entire length of the peptide. Identity can be determined by comparing each position in aligned sequences. Optimal alignment of sequences for comparisons of identity may be
 15 conducted using a variety of algorithms, as are known in the art, including the ClustalW program, available at <http://www.genome.jp/tools/clustalw/>. Sequence identity may also be determined using the BLAST algorithm. Software for performing BLAST analysis may be available through the National Center for Biotechnology Information (at <http://www.ncbi.nlm.nih.gov/>). Such algorithms that calculate percent sequence identity or
 20 homology generally account for sequence gaps and mismatches over the comparison region or area.

25 A peptide sequence is a "homologue" of, is "homologous" to, or has "homology" to another sequence if the two sequences have substantial identity over a specified region and a functional activity of the sequences is preserved or conserved, at least in part. Examples of "homologous" peptides include peptides derived from other related allergens, in particular allergens from the Cupressaceae family such as Cha o 1 and Cha o 2, and which have at least 65%, such as at least 70%, 75%, 80%, 85%, 90% or 95% identity over at least 15, 16, 17, 18, 19 or 20 contiguous amino acids or over the entire length of the peptide. Two sequences are considered to have substantially identity if, when optimally aligned (with gaps permitted),
 30 they share at least about 65% sequence identity or greater (e.g. 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identity over a specific region), for example, over all or a part of any amino acid sequence of a peptide of the invention. The percent identity can extend over the entire sequence length or a portion of the sequence.

As mentioned, a variant sequence may be a longer peptide that includes a peptide disclosed herein or a partial sequence thereof. Thus, in some embodiments a variant sequence comprises additional amino acid residues at the N- and/or C- terminal end of a peptide disclosed herein, such as additional amino acids selected from amino acids flanking the N- and/or C- terminal ends when the peptide is aligned with the allergen it is present in, based upon or derived from. Thus, where a peptide derives from the Cry j 1 allergen, the additional amino acids may be the amino acids flanking the N- and/or C-terminal ends of the peptide when aligned to allergen Cry j 1.0101 (SEQ ID No. 1). Likewise, peptides derived from Cry j 2 may comprise additional amino acids flanking the N- and/or C-terminal ends of the peptide when aligned to allergen Cry j 2.0101 (SEQ ID No. 3).

A variant sequence of the invention typically has at least 65% identity or homology over at least 15 contiguous amino acids of a peptide disclosed herein, for example least 70%, 75%, 80%, 85%, 90% or 95% identity or homology over at least 15, such as over at least 16, 17, 18, 19 or 20 contiguous amino acids of the peptide. More typically, the variant sequence has a length of 15 to 30 amino acids, and comprises an amino acid sequence having at least about 80%, such as at least about 85%, such as at least about 90% identity or homology over at least 15 contiguous amino acids of the peptide. Still more typically, the variant sequence has a length of 16 to 30 amino acids, and comprises an amino acid sequence having at least about 80%, such as at least about 85%, such as at least about 90% identity or homology over at least 16 contiguous amino acids of the peptide. Still more typically, the variant sequence has a length of 17 to 30 amino acids, and comprises an amino acid sequence having at least about 80%, such as at least about 85%, such as at least about 90% identity or homology over at least 17 contiguous amino acids of the peptide.

In one particular embodiment, a variant sequence of the invention may be a peptide selected from among those having SEQ ID Nos. 37-146 and that includes an overlap of at least 9 amino acid residues, preferably identical residues, when aligned with a peptide of the primary pool (SEQ ID Nos. 5 to 14) or a peptide of the secondary pool (SEQ ID Nos. 15 to 36). The overlap is preferably more than 9 amino acid residues, e.g. 10, 11 or 12 amino acid residues or more, such as 13, 14 or 15 amino acid residues. The core binding sequence of MHC II molecules is known to be approximately 9 amino acids long, although MHC II molecules can accommodate longer peptides of 10–30 residues (Murugan and Dai, *Immunome Research* 2005, 1:6). An overlap of 9 amino acids or more with a parent sequence is therefore sufficient for a variant sequence to be able to share a T cell epitope with the parent sequence.

In particularly, a variant sequence may comprise one, two or more lysine or arginine amino acid residue(s) added to the N- and/or C-terminus of the peptide, which may improve the aqueous solubility.

5 A variant sequence may include amino acid deletions, additions and/or substitutions, for example one to three substitutions in the amino acid sequence of the parent peptide. A variant sequence may include naturally-occurring polymorphisms or allelic variants as well as synthetic peptides that contain a limited number of amino acid substitutions in the amino acid sequence, typically conservative substitutions. Substitutions may be conservative or non-conservative amino acid substitutions.

10 A derivative of a peptide refers to a modified form of a peptide disclosed herein including a modified form of a variant sequence thereof. Typically, a derivative is formed by reacting a functional side group of an amino acid, such as a covalent or non-covalent attachment of any type of molecule (naturally occurring or designed), such as a sugar moiety. Specific examples of derivatives of a peptide include glycosylation, acetylation, phosphorylation, amidation, formylation, ubiquitination, and derivatization by protecting/blocking groups and any of numerous chemical modifications. 15 Additional specific non-limiting examples are tagged peptides, fusion peptides, chimeric peptides including peptides having one or more non-amino acyl groups (q.v., sugar, lipid, etc.) covalently linked to the peptide.

Typically, a derivative comprises one or more modifications, for example selected from any of: (a) 20 N-terminal acetylation; (b) C-terminal amidation; (c) one or more hydrogens on the side chain amines of arginine and/or lysine replaced with a methylene group; (d) glycosylation and/or (e) phosphorylation.

In particular embodiments, a derivative comprises a fusion (chimeric) sequence of peptides, which optionally may contain an amino acid sequence having one or more molecules not normally present 25 in a reference native (wild type) sequence covalently attached to the peptide amino acid sequence. The term "chimeric" and grammatical variations thereof, when used in reference to a sequence, means that the sequence contains one or more portions that are derived from, obtained or isolated from, or based upon other physical or chemical entities.

Another particular example of a derivative is one in which a second heterologous sequence, i.e. a 30 heterologous functional domain, is attached to a peptide disclosed herein, (covalent or non-covalent binding) that may confer a distinct or complementary function to a peptide disclosed herein. Heterologous functional domains are not restricted to amino acid residues. Thus, a heterologous functional domain can consist of any of a variety of different types of small or large

functional moieties. Such moieties include nucleic acid, peptide, carbohydrate, lipid or small organic compounds, such as a drug (e.g., an antiviral), a metal (gold, silver), or a radioisotope.

Linkers, such as amino acid or peptidomimetic sequences, may be inserted between the sequence and the addition (e.g., heterologous functional domain) so that the two entities maintain, at least in part, a distinct function or activity. Linkers may have one or more properties that include a flexible conformation, an inability to form an ordered secondary structure or a hydrophobic or charged character, which could promote or interact with either domain. Amino acids typically found in flexible protein regions include Gly, Asn and Ser. Other near neutral amino acids, such as Thr and Ala, may also be used in the linker sequence.

- 10 A derivative may have the same biological functionality as the peptide which is derivatized, for example have the substantially the same Class II HLA coverage.

In an embodiment disclosed herein, a peptide of formulas I, I*, II and II* comprises one or more of the modifications selected from the following:

- 15 a) N-terminal acetylation or methylation
 b) C terminal amidation
 c) C-terminal amination
 d) replacement of one or more hydrogen on the side chain amines of arginine and/or lysine with a methylene group
 e) glycosylation, and
 20 f) phosphorylation.

In an embodiment disclosed herein, any one of the peptides in the composition is a salt .

- Peptides are typically provided in the form of a salt, for example as a pharmaceutically acceptable and/or a physiologically acceptable salt. For example, the salt may be an acid addition salt with an inorganic acid, an acid addition salt with an organic acid, a salt with a basic inorganic acid, a salt with a basic organic acid, a salt with an acidic or basic amino acid or a mixture thereof. Typical examples on an acid addition salts with an inorganic acid is selected from any of salts with hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, or the like. An acid salt with an organic acid may be selected from any of salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, succinic acid, malic acid, 25 methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, or the like. Salts with an inorganic base may be selected from a salt of an alkali metal salts such as sodium salts and potassium salts; alkali earth metal salts such as calcium salts and magnesium salts; and aluminium salts and ammonium salts. Salts with a basic organic base may be selected from any salt with
- 30

trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, caffeine, piperidine, and pyridine. Salts with a basic amino acid may be selected from any salt with arginine, lysine, ornithine, or the like. Salts with an acidic amino acid may be selected from any salt with aspartic acid, glutamic acid, or the like.

In particular embodiments of the invention a salt, such as a pharmaceutically acceptable salt, is an acetate salt.

Peptides disclosed herein and variants, derivatives or salts thereof are typically manufactured synthetically. Thus, in certain embodiments peptides, or variants, derivatives and salts thereof are synthetic. The peptides, variants, derivatives and salts may be isolated and/or purified, e.g. made by the hand of man, such as by peptide synthesis. Typically, the peptides may be combined after synthesis and freeze-dried or dissolved in aqueous solutions, DMSO, glycerol or the like or mixtures thereof. Typically, each peptide of a peptide combination is present in equimolar concentrations or substantially equimolar ranges. Typically, the peptides are freeze-dried (lyophilized), such as to provide them in a storage-stable form and in a form ready to be re-dissolved. The concentration of each of the re-dissolved peptides may be in a molar concentration in the range of 1 to 1000 μM , for example in the range of 10 to 800 μM , for example in the range of 20 to 500 μM , for example in the range of 20 to 300 μM .

In particular embodiments disclosed herein, the peptides of the composition are obtained synthetically or by recombinant expression. In further embodiments disclosed herein, the peptides are freeze-dried, such as in a freeze-dried state. In further embodiments disclosed herein, each peptide in the composition is present in a molar concentration of 1 to 1000 μM , preferably 1-100 μM and more preferred in 1-10 μM . In further embodiments disclosed herein, each peptide in the composition is present in a soluble form in a molar concentration of 1 to 1000 μM preferably 1-100 μM and more preferred in 1-10 μM . In further embodiments disclosed herein, each peptide in the composition is present in equimolar concentrations or in substantially equimolar concentrations.

Further Peptide combinations

The present invention is based on an initial selection of 32 base peptides and then 28 base peptides that in combinations of three or more of these peptides as described in detail elsewhere herein are predicted to be suitable for allergy immunotherapy, where such allergy immunotherapy is expected to be efficacious for treatment of Japanese cedar pollen allergy, and optionally also allergy to related allergens such as Japanese cypress pollen, in a high percentage of a worldwide population. These first 32 base peptides *and then 28 base peptides* were selected from among a large number

of peptides either described in the literature from the cedar allergens Cry j 1 and Cry j 1, as well as from the cypress allergens Cha o 1 and Cha o 2 or as found by epitope mapping.

Based on the analysis described in the examples , a number of peptides , in total 37, were selected for mixes according to the invention.

The present invention thus provides in an aspect B peptides designed to be assembled into peptide combinations having a high worldwide HLA coverage, for example the peptides of SEQ ID Nos. 5 to 14 and optionally SEQ ID Nos. 15 to 36 disclosed herein.

The composition of this aspect of the invention may thus be defined as one comprising at least three different peptides, wherein:

(a) a first peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 9, or a variant sequence, a derivative or a salt thereof;

(b) a second peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 10 to 14, or a variant sequence, a derivative or a salt thereof; and

(c) a third peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 36 or 147, or a variant sequence, a derivative or a salt thereof.

In a further aspect, the invention provides peptide combinations comprising at least five different peptides, typically five peptides, where said five peptides consist of amino acid sequences selected from the 16-mer peptides of SEQ ID Nos. 37-146. Exemplary peptide combinations of this aspect of the invention are described in Example 6.

Such a composition may be one where the first and second peptides of (a) and (b), respectively, are:

- SEQ ID No. 5 and SEQ ID No. 10;
- SEQ ID No. 5 and SEQ ID No. 11;
- SEQ ID No. 5 and SEQ ID No. 12;
- SEQ ID No. 5 and SEQ ID No. 13;
- SEQ ID No. 5 and SEQ ID No. 14;
- SEQ ID No. 6 and SEQ ID No. 10;
- SEQ ID No. 6 and SEQ ID No. 11;
- SEQ ID No. 6 and SEQ ID No. 12;
- SEQ ID No. 6 and SEQ ID No. 13;
- SEQ ID No. 6 and SEQ ID No. 14;
- SEQ ID No. 7 and SEQ ID No. 10;
- SEQ ID No. 7 and SEQ ID No. 11;
- SEQ ID No. 7 and SEQ ID No. 12;
- SEQ ID No. 7 and SEQ ID No. 13;

- SEQ ID No. 7 and SEQ ID No. 14;
- SEQ ID No. 8 and SEQ ID No. 10;
- SEQ ID No. 8 and SEQ ID No. 11;
- SEQ ID No. 8 and SEQ ID No. 12;
- 5 • SEQ ID No. 8 and SEQ ID No. 13;
- SEQ ID No. 8 and SEQ ID No. 14;
- SEQ ID No. 9 and SEQ ID No. 10;
- SEQ ID No. 9 and SEQ ID No. 11;
- SEQ ID No. 9 and SEQ ID No. 12;
- 10 • SEQ ID No. 9 and SEQ ID No. 13;
- SEQ ID No. 9 and SEQ ID No. 14; or
- a variant sequence, a derivative or a salt of any of said sequences.

15 The third peptide (c) may be selected from among the peptides of the primary pool consisting of an amino acid sequence of SEQ ID NOS. 5 to 14, or from among the peptides of the secondary pool consisting of an amino acid sequence of SEQ ID NOS. 15 to 36, or a variant sequence, a derivative or a salt of any of these. The third peptide (c) may also be a peptide consisting of the amino acid sequence of SEQ ID No. 147, or a variant sequence, a derivative or a salt thereof.

20 The composition may optionally comprise one or more additional peptides, e.g. one, two or three further peptides, each of which may be selected from among the peptides of the primary pool consisting of an amino acid sequence of SEQ ID NOS. 5 to 14, or from among the peptides of the secondary pool consisting of an amino acid sequence of SEQ ID NOS. 15 to 36, or a peptide consisting of the amino acid sequence of SEQ ID No. 147, or a variant sequence, a derivative or a salt of any of these.

30 In a particular embodiment, a composition of the invention suitable for use in allergy immunotherapy comprises a peptide combination comprising at least four different peptides, including at least two Cry j 1 peptides and at least two Cry j 2 peptides from the primary pool (or variants, derivatives and/or salts thereof), and optionally comprising at least one additional peptide that may be selected from either the primary pool or the secondary pool.

35 In this embodiment, the composition may optionally comprise one or more additional peptides, e.g. one or two further peptides, each of which may be selected from among the peptides of the primary pool consisting of an amino acid sequence of SEQ ID NOS. 5 to 14, or from among the peptides of the secondary pool consisting of an amino acid sequence of SEQ ID NOS. 15 to 36, or a variant sequence, a derivative or a salt of any of these. The composition may e.g. comprise one additional peptide, i.e. a total of five peptides, wherein the additional peptide is selected from any

of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 36, or a variant sequence, a derivative or a salt thereof.

It will be apparent that among the peptides found in the third pool (see Table 1) there are many that substantially correspond to the peptide sequences in the primary pool and the secondary pool. From this alignment to SEQ ID NO 1 and 2 or SEQ ID NO 3 and 4 it is apparent that the similar peptides from SEQ ID Nos. 37-146 can be considered to be specific examples of "variant" sequences of the respective peptides of SEQ ID Nos. 5-36. The following Table B illustrates by way of example peptides of the primary pool, and corresponding exemplary variant sequences from the peptides of SEQ ID Nos. 37-146 as an example.

Table B – Exemplary sequence variants of primary pool peptides

Primary pool peptide (SEQ ID No.)	Exemplary variants (SEQ ID No.)
5	59, 58
6	66
7	69, 68
8	76, 75, 77
9	77, 78
10	98
11	107
12	113
13	119
14	132, 131

Variant sequences of the secondary pool peptides (SEQ ID Nos. 15-36) from the peptides of SEQ ID Nos. 37-146 may be readily identified in the same manner.

As noted above, a composition of the invention will comprise at least three peptides. The composition may for example comprise 3, 4, 5, 6, 7, 8, 9 or 10 peptides. In determining the optimal number of peptides in a composition of the invention, it is preferred on the one hand that the composition has a sufficient number of peptides to make it likely to be efficacious in most or preferably substantially all Japanese cedar pollen allergy patients, i.e. in terms of efficacy a larger number of peptides is advantageous. On the other hand, there are other factors that make it desirable to limit the number of peptides in a composition. These include e.g. cost considerations, formulation considerations (e.g. designing a formulation in which different peptides with different isoelectric points are all soluble), and regulatory challenges involved in obtaining approval for compositions of increased complexity. Weighing these opposing factors, the composition of the

invention will preferably include four, five or six peptides, as it is believed that such a composition will be on the one hand efficacious in a large majority of patients while on the other hand sufficiently limited in peptide number that potential cost, formulation and regulatory challenges will be manageable.

5

In an aspect of the invention compositions are provided comprising a peptide combination comprising at least five different peptides, where said at least five peptides consist of amino acid sequences:

- SEQ ID Nos. 106, 63, 77, 112 and 53;
- 10 • SEQ ID Nos. 106, 63, 87, 56 and 85;
- SEQ ID Nos. 106, 63, 100, 49 and 124;
- SEQ ID Nos. 106, 63, 113, 62 and 123;
- SEQ ID Nos. 106, 63, 107, 59 and 68;
- SEQ ID Nos. 100, 77, 53, 123 and 85;
- 15 • SEQ ID Nos. 100, 77, 119, 49 and 124;
- SEQ ID Nos. 100, 77, 110, 48 and 84;
- SEQ ID Nos. 100, 77, 97, 107 and 73;
- SEQ ID Nos. 100, 77, 98, 59 and 129;
- SEQ ID Nos. 112, 53, 123, 56 and 95;
- 20 • SEQ ID Nos. 112, 53, 124, 85 and 62;
- SEQ ID Nos. 112, 53, 107, 87 and 81;
- SEQ ID Nos. 112, 53, 84, 97 and 59;
- SEQ ID Nos. 112, 53, 119, 52 and 48;
- SEQ ID Nos. 87, 49, 85, 48 and 123;
- 25 • SEQ ID Nos. 87, 49, 119, 62 and 56;
- SEQ ID Nos. 87, 49, 107, 97 and 73;
- SEQ ID Nos. 87, 49, 124, 129 and 95;
- SEQ ID Nos. 87, 49, 110, 84 and 58;
- SEQ ID Nos. 123, 119, 48, 95 and 56;
- 30 • SEQ ID Nos. 123, 119, 73, 62 and 107;
- SEQ ID Nos. 123, 119, 58, 125 and 52;
- SEQ ID Nos. 123, 119, 81, 59 and 85;
- SEQ ID Nos. 123, 119, 82, 64 and 84;
- SEQ ID Nos. 107, 48, 124, 95 and 85;
- 35 • SEQ ID Nos. 107, 48, 97, 56 and 125;
- SEQ ID Nos. 107, 48, 110, 62 and 59;
- SEQ ID Nos. 107, 48, 132, 129 and 52; or
- a variant sequence, a derivative or a salt of any of said sequences.

Concerning variants of the above-mentioned parent peptides, see variant description above.

Pharmaceutical compositions

- 5 The invention also features a pharmaceutical composition comprising a composition, e.g. a peptide combination defined herein. The pharmaceutical composition may be a product, such as a vaccine for allergy immunotherapy, including but not limited to immunotherapy to treat an allergic immune response or allergic disease to Japanese cedar pollen.

10 A pharmaceutical composition comprises in addition to the peptide combination one or more pharmaceutically acceptable or physiologically acceptable excipient(s), carriers and/or adjuvants, which usually are therapeutically inactive ingredients. Excipients for use in pharmaceutical compositions are well-known to the person skilled in the art and include , but are not limited to, solvents, emulsifiers, wetting agents, plasticizers, solubilizers (e.g. solubility enhancing agents), colouring substances, fillers, preservatives, anti-oxidants, anti-microbial agents, viscosity adjusting
15 agents, buffering agents, pH adjusting agents, isotonicity adjusting agents, mucoadhesive substances, and the like. Examples of formulation strategies are well known to the person skilled in the art.

In some embodiments, the peptide may be formulated (e.g. mixed together) with immune-modifying agents such as adjuvants. The adjuvant(s) may be selected from any conventional
20 adjuvant, including but not limited to oxygen-containing metal salts, e.g. aluminium hydroxide, aluminium phosphate, chitosan, heat-labile enterotoxin (LT), cholera toxin (CT), cholera toxin B subunit (CTB), polymerized liposomes, mutant toxins, e.g. LTK63 and LTR72, microcapsules, interleukins (e.g. IL-1 beta, IL-2, IL-7, IL-12), IFN-gamma, GM-CSF, MDF derivatives, CpG oligonucleotides, LPS, MPL, MPL-derivatives, phosphophazenes, Adju-Phos(R), glucan, antigen
25 formulations, liposomes, DDE, DHEA, DMPC, DMPG, DOC/Alum Complex, Freund's incomplete adjuvant, ISCOMs(R), LT Oral Adjuvant, muramyl dipeptide, monophosphoryl lipid A, muramyl peptide and phosphatidylethanolamine. Additional examples of adjuvants are described, for example, in "Vaccine Design--the subunit and adjuvant approach" (Edited by Powell, M. F. and Newman, M. J.; 1995, Pharmaceutical Biotechnology (Plenum Press, New York and London, ISBN 0-306-44867-
30 X) entitled "Compendium of vaccine adjuvants and excipients" by Powell, M. F. and Newman M.

Typically, the pharmaceutical composition is a liquid, such as a solution, a suspension, a dispersion or a gelled liquid. Furthermore, the composition may be an emulsion, a powder, for example a re-

dissolvable powder, a granulate or a lyophilizate, which may be dissolved to form a liquid before being administered.

The pharmaceutical composition is typically provided as a powder, for example freeze-dried.

Typically, the freeze-dried composition is adapted to be re-dissolved before use, for example re-

- 5 dissolved in an aqueous, normally sterile, solution, for example a solution having a pH in the range of 3 to 9, such as pH in the range of 3 to 8, such as pH in the range of 4 to 8.

Alternatively, the pharmaceutical composition may be a solid dosage form, such as a tablet such as a freeze dried tablet formulation for fast disintegration, or a capsule. Pharmaceutical formulations and delivery systems appropriate for the compositions, methods and uses of the invention are

- 10 known in the art (see, e.g., Remington: The Science and Practice of Pharmacy (2003) 20th ed., Mack Publishing Co., Easton, PA; Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing Co., Easton, PA; The Merck Index (1996) 12th ed., Merck Publishing Group, Whitehouse, NJ; Pharmaceutical Principles of Solid Dosage Forms (1993), Technomic Publishing Co., Inc., Lancaster, Pa.; Ansel and Soklosa, Pharmaceutical Calculations (2001) 11th ed., Lippincott Williams & Wilkins, Baltimore, MD; and Poznansky et al., Drug Delivery Systems (1980), R. L. Juliano, ed.,
15 Oxford, N.Y., pp. 253-315).

Pharmaceutical compositions can be formulated to be compatible with a particular route of administration. Thus, pharmaceutical compositions may include carriers, diluents, or excipients suitable for administration by various routes.

- 20 In some embodiments, the pharmaceutical composition is aqueous, while in other embodiments the composition may be in the form of non-aqueous solutions, suspensions or emulsions of the peptides, which compositions are typically sterile and can be isotonic with the biological fluid or organ of the intended recipient. Furthermore, the pH of an aqueous solution is typically in the range of 3 to 9, such as 3 to 8, such as 4 to 8. Non-limiting examples of formulation ingredients include
25 water, saline, dextrose, fructose, ethanol, vegetable or synthetic oils.

For oral, buccal or sublingual administration, a composition can take the form of, for example, tablets or capsules, optionally formulated as fast-integrating tablets/capsules or slow-release tablets/capsules. In some embodiments, the tablet is a freeze-dried, optionally a fast-disintegrating tablet suitable for being administered under the tongue.

- 30 The pharmaceutical composition may also be formulated into a "unit dosage form", which as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of a peptide or peptide combination, optionally in

association with a pharmaceutical carrier (excipient, diluent, vehicle or filling agent) which, when administered in one or more doses, is calculated to produce a desired effect. Unit dosage forms also include, for example, ampules and vials, which may include a composition in a freeze-dried or lyophilized state; a sterile liquid carrier can be added prior to administration or delivery *in vivo*.

5 Unit dosage forms additionally include, for example, ampules and vials with liquid compositions disposed therein.

In some embodiments, the pharmaceutical composition may be formulated for parenteral administration, such as formulated for injection, e.g. subcutaneous and/or intradermal injection. Therefore, in some embodiments, the pharmaceutical composition may be a liquid (i.e. formulated as a liquid), including a solution, a suspension, a dispersion, and a gelled liquid. For example, a liquid pharmaceutical composition may be formed by dissolving a powder, granulate or lyophilizate of a peptide combination described herein in a suitable solvent and then administering to a subject. Suitable solvents may be any solvent having physiologically acceptable properties and able to dissolve the peptide combination in desired concentrations. A desired concentration may depend on the aliquot to be administered (i.e. to be injected) and the desired single dose. It is emphasized that for the purposes of injection the aliquot is in the range of about 10 to 500 microliters, e.g. 50 to 300 microliters or less and a desired single dose is within range of 1 to 1000 nanomole. Therefore, a suitable solvent should be able to dissolve any peptide of the combination to achieve a final concentration of about 1 to 1000 μM for each of the peptides. Thus, in one embodiment, a liquid composition comprises each of the peptides of the combination in a concentration of 10 to 800 μM , for Example 20 to 500 μM or 20 to 300 μM . Typically, the concentration of each peptide is the same, such as in an equimolar concentration, but each peptide of the composition may be present in different concentrations. Typically, the solvent is an aqueous solution, optionally mixed with other solvents. Thus, a solvent may comprise at least 60% w/w of water, e.g. at least 65% w/w, 70% w/w, 75% w/w, 80% w/w, 85% w/w, 90% w/w or 95% w/w, 99% w/w of water, such as distilled water, such as sterile water. In some embodiments, the solvent is sterile distilled water, e.g. water for injection. An aqueous solution may comprise other solvents than water, for example DMSO (dimethylsulfoxide), glycerol, ethanol, acetonitrile, vegetable or synthetic oils. The pH of the aqueous phase of the solvent may be in a physiological acceptable range, typically in the range of 3 to 9, such as in the range of pH 3 to 8, such as in the range of pH 4 to 8, such as in the range of 5 to 8, such as in the range of 6 to 8. Thus, the liquid formulation may comprise a pH controlling agent or buffering agent (e.g. citrate buffer, phosphate buffer, acetate buffer), optionally the pH may be adjusted with dilutions of strong base (e.g. sodium hydroxide or the like) and/or dilutions of strong acids (e.g. hydrochloric acid).

35 Typically, the liquid formulation is isotonic, and optionally sterile. Therefore, in some embodiments, the formulation comprises saline, such as isotonic saline. The liquid may contain additional

excipients, such as another solvent, a solubilizing enhancing agent (e.g. polyoxyethylene (20) sorbitan monolaurate (Tween® 20)), ionic and non-ionic emulsifiers (e.g. poloxamers (Kolliphor®)), a dispersant, a thickener, a preservative, an anti-microbial agent, and/or an antioxidant. Non-limiting illustrative examples of solvents include water, saline, DMSO, glycerol, ethanol, acetonitrile, vegetable or synthetic oils.

Some peptides are known to be prone to oxidation or being unstable when exposed to water for a long period. Therefore, to achieve storage stable compositions, a pharmaceutical composition may be formulated to contain only a limited amount of water or aqueous solution, e.g. containing less than 10% w/w of water or aqueous solution, such as less than 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5% w/w of water or aqueous solution. Examples of pharmaceutical compositions with limited levels of water may include granulates, powders, for example lyophilizates, i.e. freeze-dried powders. Typically, the freeze-dried composition may be dissolved before use, for example dissolved in an aqueous, optionally sterile, solution, for example a solution having a pH in the range of 3-9, such as pH in the range of 3 to 8, such as pH in the range of 4 to 8. A lyophilizate may contain additional ingredients, e.g. bulking agents and lyoprotectants (e.g. sucrose, lactose, trehalose, mannose, mannitol, sorbitol, glucose, raffinose, glycine, histidine or mixtures thereof), buffering agents (e.g. sodium citrate, sodium phosphate, disodium phosphate, sodium hydroxide, Tris base, Tris acetate, Tris HCl or mixtures thereof), antioxidants, antimicrobial agents, solubilizers (e.g. polyoxyethylene (20) sorbitan monolaurate (Tween® 20)).

A freeze-dried composition may also be formulated into a solid dosage form that is administered for example by the oral route such as by oral mucosa. Thus, in some embodiments, the pharmaceutical composition may be formulated for oral administration, for example for sublingual administration. Therefore, the pharmaceutical composition may be a solid dosage form, such as a freeze-dried solid dosage form, typically a tablet, a capsule or sachet, which optionally may be formulated for fast disintegration. Pharmaceutical formulations and delivery systems appropriate for the compositions, methods and uses of the invention are known in the art (see, e.g., Remington: The Science and Practice of Pharmacy (2003) 20th ed., Mack Publishing Co., Easton, PA; Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing Co., Easton, PA; The Merck Index (1996) 12th ed., Merck Publishing Group, Whitehouse, NJ; Pharmaceutical Principles of Solid Dosage Forms (1993), Technomic Publishing Co., Inc., Lancaster, Pa.; Ansel and Soklosa, Pharmaceutical Calculations (2001) 11th ed., Lippincott Williams & Wilkins, Baltimore, MD; and Poznansky et al., Drug Delivery Systems (1980), R. L. Juliano, ed., Oxford, N.Y., pp. 253-315).

As mentioned, pharmaceutical compositions can be formulated to be compatible with a particular route of administration, such as by intradermal or by sublingual administration. Thus, pharmaceutical compositions may include carriers, diluents, or excipients suitable for administration

by various routes. Exemplary routes of administration for contact or in vivo delivery for which a composition can optionally be formulated include inhalation, intranasal, oral, buccal, sublingual, subcutaneous, intradermal, epicutaneous, rectal, transdermal, or intralymphatic.

For oral, buccal or sublingual administration, a composition may take the form of, for example, tablets or capsules, optionally formulated as fast-disintegrating tablets/capsules or slow-release tablets/capsules. In some embodiments, the tablet is freeze-dried, optionally a fast-disintegrating tablet or capsule suitable for being administered under the tongue.

The pharmaceutical composition may also be formulated into a "unit dosage form", which used herein refers to physically discrete units, wherein each unit contains a predetermined quantity of a peptide or peptide combination, optionally in association with a pharmaceutical carrier (excipient, diluent, vehicle or filling agent) which, when administered in one or more doses, may produce a desired effect. Unit dosage forms also include, for example, ampules and vials, which may include a composition in a freeze-dried or lyophilized state (a lyophilizate) or a sterile liquid carrier, for example that can be added prior to administration or delivery in vivo. Unit dosage forms additionally include, for example, ampules and vials with liquid compositions disposed therein.

Peptides may be prone to degradation when exposed to oxygen, for example when exposed to air or solvents containing air. Therefore, in some embodiments, the pharmaceutical composition comprises an inert gas, e.g. argon or nitrogen.

Another aspect of the invention relates to a kit comprising a compartment and instructions, wherein the compartment comprises a composition, e.g. a peptide combination defined herein, or a pharmaceutical composition defined herein and wherein the instructions are for use in treating allergy to Japanese cedar pollen or pollen having cross reactivity to Japanese cedar pollen. A kit may further comprise packaging material comprising corrugated fibre, glass, plastic, foil, ampules, vials, blister pack, preloaded syringes or tubes, optionally that maintain sterility of the components. A kit may further comprise labels or inserts comprising printed matter or computer readable medium optionally including identifying components, dose amounts, clinical pharmacology and instructions for the clinician or for a subject using one or more of the kit components, prophylactic or therapeutic benefits, adverse side effects or manufacturer information.

In one embodiment, the kit additionally comprises a container comprising a solvent for dissolving the composition before use. Examples of suitable solvents are described supra. Optionally, the kit may also comprise a device for use in parenteral injection, e.g. for injecting the composition (e.g. dissolved composition) to a subcutaneous or intradermal tissue. A device may be any suitable device for that purpose, such as a needle or microneedle adapted for intradermal or subcutaneous

delivery of the composition. For example, the device may be a microneedle or a device comprising a plurality of microneedles designed for intradermal delivery of liquids, e.g. as described in international patent applications WO14064543 A1, WO05049107 A2, WO06054280 A2, WO07066341 A3 and WO14188429 A1.

- 5 Pharmaceutical compositions of peptide combinations are further described by the embodiments cited in the claims defined herein, which embodiments may be combined in any order.

Therapy

- 10 As set forth above, an aspect of the invention relates to a method of treating allergy to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a composition, a pharmaceutical composition or a kit described herein.

- 15 In other words, an aspect of the invention relates to a method of treating allergy in a subject in need thereof, where signs and/or symptoms of said allergy are elicited by exposure to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a composition, a pharmaceutical composition or a kit described herein.

- 20 It should be understood that the present aspect also relates to a composition, a pharmaceutical composition or a kit described herein for use in treating allergy to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof, such as for use in treating allergy in a subject in need thereof, where signs and/or symptoms of said allergy are elicited by exposure to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof.

- 30 Likewise, the present aspect also relates to the use of a composition, a pharmaceutical composition or a kit described herein for the preparation of a medicament for use for use in treating allergy to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof, such as for use in treating allergy in a subject in need thereof, where signs and/or symptoms of said allergy are elicited by exposure to Japanese cedar pollen (e.g. to an

allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) in a subject in need thereof.

Regarding signs or symptoms of allergy, cf. below for further discussion, but it is generally

5 understood that this means signs or symptoms of IgE mediated allergy including that the patient has elicited IgE-antibodies against an allergen of Japanese cedar pollen or of pollen cross-reactive with Japanese cedar pollen.

While true prophylaxis of allergy is not excluded when carrying out the method of treatment, it is expected that the method will find particular use in patients that have already experienced cedar
10 pollen allergy or have raised IgE antibodies against a cedar pollen allergen. Therefore, all embodiments may entail or consist of treating the allergy by relieving or reducing an immune response triggered by exposure to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen). Also, treating the allergy can in all embodiments of the
15 present aspect comprise or consist of relieving one or more signs/symptoms of an immune response triggered by exposure to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen). Moreover, treating the allergy may in all embodiments of the present aspect consist of or comprise induction of immunological tolerance against Japanese
20 cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen). And treating the allergy may in all embodiments of the present aspect comprise or consist of relieving one or more signs/symptom(s) associated with allergic rhinitis and/or allergic conjunctivitis and/or allergic asthma and/or allergic eczema (e.g. atopic dermatitis).

25 The signs/symptoms of allergy mentioned above are those typically associated with the allergies treated according to the present invention, typically signs/symptoms may include one or more of the following; itchy running nose, itchy watery eyes, itchy skin and shortness of breath and the patient may experience that the signs/symptoms will to some extent be relieved by treatment with antihistamines or steroids. In a clinical setting, the signs and symptoms may include detectable
30 levels of IgE antibodies against one or more Japanese cedar pollen allergens or cross reacting allergens of interest.

Thus, compositions disclosed herein may produce a therapeutic or beneficial effect, which optionally may be objectively or subjectively measurable. A therapeutic or beneficial effect can but need not

be complete ablation of all or any immune response, or one or more symptoms caused by or associated with an allergen. Thus, a satisfactory clinical result is achieved when there is an incremental improvement or a partial reduction in an immune response or one or more symptoms caused by or associated with an allergen, or there is an inhibition, decrease, reduction,

- 5 suppression, prevention, limit or control of worsening or progression of an immune response or one or more symptoms caused by or associated with an allergen over a short or long duration (hours, days, weeks, months, etc.).

In the event that the treatment entails or consists of relieving one or more signs or symptoms associated with allergic rhinitis, the relief is typically

- 10 - reduction of the intensity of itchy nose and/or
 - reduction of the number of sneezes within a given period (e.g. daily, weekly, monthly) and/or
 - reduction of the intensity of blocked nose (congestion) and/or
 - reduction of the amount of nasal fluid and/or
 - reduction of the eosinophilic count in nasal fluid and/or
 15 - reduction of specific IgE antibody level (titre) in nasal fluid or in serum and/or
 - reduction of basophil histamine release in blood.

It is to be noted that a "sign" of allergy is an objectively observable characteristic of the disease, whereas a "symptom" is the patient's subjective experience(s) relative to the disease. Some signs can be symptoms and vice versa, but if a patient for instance experiences dizziness due to a
 20 disease, this can only be categorized as a symptom, because it is not objectively observable by anybody else than the patient. On the other hand, increasing levels of for example IgE-antibodies is a "sign", since it cannot be sensed by the patient but it can be objectively measured in an appropriate assay.

Where treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic conjunctivitis, the relief typically comprises

- 25 - reducing the intensity of itchy eyes, redness in the white of the eyes and/or watery eyes; and/or
 - reducing the eosinophilic count in conjunctival tissue scrapings; and/or
 - reducing specific IgE antibody level (titer) in conjunctival tissue scrapings or in serum; and/or
 -reducing basophil histamine release in blood.

Where treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic asthma, the relief typically comprises

- 30 - reducing the intensity and/or number of coughs within a given period (e.g. daily, weekly, monthly); and/or
 - reducing the intensity of wheezes; and/or

- improving being short of breath; and/or
- improving lung function; and/or
- reducing specific IgE antibody level (titre) in lung fluid or in serum; and/or
- reducing basophil histamine release in blood.

- 5 Where treating the allergy comprises or consists of relieving one or more signs or symptoms associated with atopic dermatitis, the relief typically comprises
- reducing itch intensity of the skin; and/or
 - reducing eczema score; and/or
 - reducing number of (peripheral) blood eosinophils.
- 10 In all embodiments of the present aspect of the invention, the method may comprise or consist of reducing the patient's need for concomitant treatment with corticosteroids or H1 antihistamines to reduce, relieve, or suppress one or more symptoms of an immune response associated with the allergy. In other words, these embodiments have the long term benefit of reducing the patient's need for medication.
- 15 As used herein, the term "immunological tolerance" refers to a) a decreased or reduced level of a specific immunological response (thought to be mediated at least in part by antigen-specific effector T lymphocytes, B lymphocytes, antibodies, or a combination thereof); b) a delay in the onset or progression of a specific immunological response; or c) a reduced risk of the onset or progression of a specific immunological response to mites. An increase, improvement,
- 20 enhancement or induction of "tolerance" may refer to a decrease, reduction, inhibition, suppression, or limiting or controlling or clearing of specific immunological reactivity to an allergen as compared to reactivity to the allergen in a previous exposure to the same allergen. Thus, in certain embodiments, the method comprises inducing immunological tolerance in a subject to Japanese cedar pollen (e.g. to an allergen of Japanese cedar pollen) or to pollen cross-reactive with
- 25 Japanese cedar pollen (e.g. to an allergen cross reacting with an allergen of Japanese cedar pollen) to suppress an allergic immune response to the allergen. Immunological tolerance in a subject to an allergen can also be reflected by reducing the occurrence, frequency, severity, progression, or duration of an allergic response of the subject to the allergen. Induction of immune tolerance (also referred to as desensitization), and the relative amount of immune tolerance, can be measured by
- 30 methods disclosed herein or known to the skilled artisan. For example, induction of immune tolerance can be measured by the modulated lymphokine and/or cytokine level in a subject or animal before versus after administering a peptide combination described herein for the first time. A modulated cytokine level can be an increase of a cytokine level, for instance an increase of a lymphokine and/or cytokine level of at least 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 20, 50 times or more
- 35 relative to before administering the peptide combination for the first time. Alternatively, modulation

can be a decrease of the level of a particular cytokine level, for instance a decrease of the lymphokine and/or cytokine level of at least 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 20, 50 times or more relative to before administering a peptide combination for the first time. The lymphokines/cytokines chosen to be measured can be from any relevant lymphokines/cytokines, such as IL-2, IL-5, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, TNF-alfa, IFN-gamma, TGF-beta, MCP-1, RANK-L and Flt3L. Accordingly, the term "inducing immunological tolerance" may include eliciting, stimulating, promoting, increasing or enhancing immunological tolerance. Immunological tolerance may involve modulation of T cell activity, including but not limited to CD4+ T cells, CD8+ T cells, Th1 cells, Th2 cells and regulatory T cells (Tregs), and memory T cells, including inflammatory lymphokines/cytokines produced by T cells.

Therefore, in some embodiments of the present aspect, the method comprises decreasing a T cell response in the patient/subject in need thereof against an allergen of Japanese cedar or a cross reacting allergen.

The patients/subjects subjected to the treatment of the present aspect of the invention typically present with an immune response clinically presented as atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anapylaxis, and/or hay fever. In particular advantageous versions of any one of the embodiments of the present aspect of the invention, the treatment thus decreases, reduces, suppresses or inhibits atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anaphylaxis, and/or hay fever.

Therefore, in still other aspects, the subject's administration of a therapeutically effective amount of a composition described herein may relieve one or more symptoms of the immune response. For example, the method may comprise relieving one or more symptoms associated with allergic rhinitis, allergic conjunctivitis, allergic asthma and/or allergic eczema (e.g. atopic dermatitis).

It will be understood that the patients that are subjected to the method of the present aspect of the invention are typically sensitized to at least one allergen of Japanese cedar pollen, e.g. Cry j 1 and/or Cry j 2 or a cross reacting allergen of Cry j 1 and/or Cry j 2. It is to be understood that such patients/subjects may exhibit allergy signs or experience symptoms of allergy, but it is not excluded that subjects which do not exhibit clinical relevant allergy signs allergy will also benefit from the treatment.

The allergy treated according to the invention is in all embodiments of the present aspect of the invention allergy towards Japanese cedar pollen and optionally to pollen cross-reactive with Japanese cedar pollen. Japanese cedar pollen may be from the genus *Cryptomeria*, such as from the species *Cryptomeria japonica*. Allergens cross-reactive with allergens of Japanese cedar pollen

may be allergens of the Cupressaceae family. It is known (see e.g. Schwietz et al., *Ann. Allergy Asthma Immunol.* 2000, 84:87-93) that there is considerable cross-reactivity among antibodies against pollen allergens from a number of species within the Cupressaceae family, and between Japanese cedar (which belongs to the Taxodiaceae family) and members of the Cupressaceae family. References herein to "cross-reactive pollen allergens" include pollen of such "cross-reactive" species, especially cross-reactive pollen allergens of Cupressaceae species. Such cross-reactive species include, but are not limited to, the following:

- *Juniperus ashei* (Mountain cedar)
- *Juniperus californica* (California juniper)
- *Juniperus chinensis* (Chinese juniper)
- *Juniperus scapulorum* (Rocky Mountain cedar)
- *Juniperus osteosperma* (Utah juniper)
- *Juniperus monosperma* (One-seed juniper)
- *Juniperus pinchotti* (Pinchot juniper)
- *Juniperus occidentalis* (Hooker western juniper)
- *Juniperus virginiana* (Eastern red cedar)
- *Libocedrus decurrens* (Incense cedar)
- *Cupressus arizonica* (Arizona cypress)
- *Chamaecyparis lawsonia* (Port Orford cedar)
- *Chamaecyparis obtusa* (Japanese cypress)

As indicated above, one species of particular interest in the context of the present invention whose pollen gives rise to antibodies that are cross-reactive with Japanese cedar pollen is Japanese cypress (*Chamaecyparis obtusa*). This is related to the fact that the amino acid sequences of the relevant pollen allergens have a high degree of similarity between the two species. Thus, the amino acid sequence of the Cha o 1 allergen from Japanese cypress has 79-80% identity with the sequence of the Cry j 1 allergen from Japanese cedar (Suzuki et al., *Mol Immunol.* 1996, 33(4-5):451-60), while the amino acid sequence of the Cha o 2 allergen from Japanese cypress has 74% identity with the sequence of the Cry j 2 allergen from Japanese cedar (Mori et al., *Biochem Biophys Res Commun.* 1999, 263(1):166-71). It is known that there is a high degree of "cross-reactivity" between allergens from pollen of Japanese cedar and Japanese cypress, resulting in persistent allergic symptoms in more than 70% of Japanese cedar pollen allergy patients in Japan even after the pollen season for Japanese cedar has ended, with sensitization with cedar pollen playing a direct role in the prolonged allergic symptoms experienced during the cypress pollen season (Sone et al., *Clin. Exp. Allergy* 2005, 35:664-671; Sone et al., *Allergology Int.* 2009, 58:237-245).

It has also been found that the allergens Jun a 1 (*J. ashei*), Jun v 1 (*J. virginiana*), Cup a 1 (*C. arizonica*) and Cup s 1 (*C. sempervirens*) have a high degree of sequence identity, up to 81–96%, to each other and to Cha o 1 and Cry j 1 (Sone et al., *Clin. Exp. Allergy* 2005). It is therefore contemplated that peptide compositions of the invention for treatment of allergy to Japanese cedar pollen may also be effective in treating and preventing allergy to pollen of these and other members of the cypress family.

Thus, pollen cross-reactive with Japanese cedar pollen is selected from pollen of the Cupressaceae family, such as from pollen of Japanese cypress (*Chamaecyparis obtuse*), Common cypress (*Cupressus sempervirens*) and Mountain cedar (*Juniperus ashei*). An allergen of Japanese cedar pollen may be Cry j 1 and/or Cry j 2, whereas an allergen cross reacting with Cry j 1 may be Cha o 1, Jun a 1 and/or Cup s 1 and an allergen cross reacting with Cry j 2 may be Cha o 2, Jun a 2 and/or Cup s 2.

The composition to be administered may be administered by the parenteral route to the patient/subject in need thereof, such as via a route of administration selected from any one of subcutaneous, intradermal, epicutaneous, topical, sublingual, buccal, intranasal, respiratory and the intralymphatic route. In particular the intradermal route of administration is of interest.

Typically, the subject in need thereof is a human, a pet such as a dog or a cat, a domestic animal such as a horse, or a laboratory animal (a mouse, a guinea pig or a rabbit). The subject may be sensitized to Japanese cedar pollen or cross reactive pollen (e.g. the subject have specific IgE antibodies against an allergen of Japanese cedar pollen and/or have a T cell response against an allergen of Japanese cedar pollen).

Typically, a composition is administered several times, i.e. repeatedly, such as in weekly, bi-weekly, monthly or quarterly intervals. As will be understood from the above, the allergy is, according to the present aspect of the invention and any embodiments thereof, preferably treated by immunotherapy. The patient in question need not be human. As such, the patient may be human or a mammal, such as a cat, dog, and a horse.

A pharmacologically effective amount of a single dose of a polypeptide of the first aspect or a composition of the second aspect may be in the range of 1 to 1000 nanomole, for example 1 to 500 nanomole, for example 1 to 250 nanomole, for example 5 to 250 nanomole. Typically, a polypeptide or composition of the invention is administered as a liquid in a volume of about 50 to 150 microliter, such as by intradermal administration.

A another aspect of the invention relates to an *in-vitro* method of determining whether T cells of a subject in need of treatment recognize a composition as described herein, comprising contacting T cells obtained from the subject with said composition or a single peptide thereof and detecting whether the T cells are stimulated by said composition or single peptide. The *in-vitro* method may be used to determine whether the subject has, or is at risk of developing, an allergy to Japanese cedar pollen or cross reacting pollen.

The application further relates to the following embodiments A:

Embodiment 1. A composition comprising a peptide combination comprising at least three different peptides, wherein

(a) a first peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 9, or a variant sequence, a derivative or a salt thereof;

(b) a second peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 10 to 14, or a variant sequence, a derivative or a salt thereof; and

(c) a third peptide is selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 36 or 147, or a variant sequence, a derivative or a salt thereof.

Embodiment 2. The composition of embodiment 1, where peptides (a) and (b), respectively, are:

- SEQ ID No. 5 and SEQ ID No. 10;
- SEQ ID No. 5 and SEQ ID No. 11;
- SEQ ID No. 5 and SEQ ID No. 12;
- SEQ ID No. 5 and SEQ ID No. 13;
- SEQ ID No. 5 and SEQ ID No. 14;
- SEQ ID No. 6 and SEQ ID No. 10;
- SEQ ID No. 6 and SEQ ID No. 11;
- SEQ ID No. 6 and SEQ ID No. 12;
- SEQ ID No. 6 and SEQ ID No. 13;
- SEQ ID No. 6 and SEQ ID No. 14;
- SEQ ID No. 7 and SEQ ID No. 10;
- SEQ ID No. 7 and SEQ ID No. 11;
- SEQ ID No. 7 and SEQ ID No. 12;
- SEQ ID No. 7 and SEQ ID No. 13;
- SEQ ID No. 7 and SEQ ID No. 14;
- SEQ ID No. 8 and SEQ ID No. 10;
- SEQ ID No. 8 and SEQ ID No. 11;
- SEQ ID No. 8 and SEQ ID No. 12;
- SEQ ID No. 8 and SEQ ID No. 13;
- SEQ ID No. 8 and SEQ ID No. 14;

- SEQ ID No. 9 and SEQ ID No. 10;
- SEQ ID No. 9 and SEQ ID No. 11;
- SEQ ID No. 9 and SEQ ID No. 12;
- SEQ ID No. 9 and SEQ ID No. 13;
- 5 • SEQ ID No. 9 and SEQ ID No. 14; or
- a variant sequence, a derivative or a salt of any of said sequences.

Embodiment 3. The composition of embodiment 1 or 2, comprising at least one additional peptide selected from any of peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 14 or SEQ ID NOs. 15 to 36, or a variant sequence, a derivative or a salt thereof.

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Embodiment 4. The composition of embodiment 3, comprising one, two or three additional peptides.

Embodiment 5. A composition comprising a peptide combination comprising at least four different peptides, wherein

15

(a) a first peptide and a second peptide are selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 9, or a variant sequence, a derivative or a salt thereof; and

(b) a third peptide and a fourth peptide are selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 10 to 14, or a variant sequence, a derivative or a salt thereof.

20

Embodiment 6. The composition of embodiment 5, wherein the first, second, third and fourth peptides, respectively, are:

- SEQ ID Nos. 5, 6, 10 and 11;
- SEQ ID Nos. 5, 6, 10 and 12;
- 25 • SEQ ID Nos. 5, 6, 10 and 13;
- SEQ ID Nos. 5, 6, 10 and 14;
- SEQ ID Nos. 5, 6, 11 and 12;
- SEQ ID Nos. 5, 6, 11 and 13;
- SEQ ID Nos. 5, 6, 11 and 14;
- 30 • SEQ ID Nos. 5, 6, 12 and 13;
- SEQ ID Nos. 5, 6, 12 and 14;
- SEQ ID Nos. 5, 6, 13 and 14;
- SEQ ID Nos. 5, 7, 10 and 11;
- SEQ ID Nos. 5, 7, 10 and 12;
- 35 • SEQ ID Nos. 5, 7, 10 and 13;
- SEQ ID Nos. 5, 7, 10 and 14;

- SEQ ID Nos. 5, 7, 11 and 12;
- SEQ ID Nos. 5, 7, 11 and 13;
- SEQ ID Nos. 5, 7, 11 and 14;
- SEQ ID Nos. 5, 7, 12 and 13;
- 5 • SEQ ID Nos. 5, 7, 12 and 14;
- SEQ ID Nos. 5, 7, 13 and 14;
- SEQ ID Nos. 5, 8, 10 and 11;
- SEQ ID Nos. 5, 8, 10 and 12;
- SEQ ID Nos. 5, 8, 10 and 13;
- 10 • SEQ ID Nos. 5, 8, 10 and 14;
- SEQ ID Nos. 5, 8, 11 and 12;
- SEQ ID Nos. 5, 8, 11 and 13;
- SEQ ID Nos. 5, 8, 11 and 14;
- SEQ ID Nos. 5, 8, 12 and 13;
- 15 • SEQ ID Nos. 5, 8, 12 and 14;
- SEQ ID Nos. 5, 8, 13 and 14;
- SEQ ID Nos. 5, 9, 10 and 11;
- SEQ ID Nos. 5, 9, 10 and 12;
- SEQ ID Nos. 5, 9, 10 and 13;
- 20 • SEQ ID Nos. 5, 9, 10 and 14;
- SEQ ID Nos. 5, 9, 11 and 12;
- SEQ ID Nos. 5, 9, 11 and 13;
- SEQ ID Nos. 5, 9, 11 and 14;
- SEQ ID Nos. 5, 9, 12 and 13;
- 25 • SEQ ID Nos. 5, 9, 12 and 14;
- SEQ ID Nos. 5, 9, 13 and 14;
- SEQ ID Nos. 6, 7, 10 and 11;
- SEQ ID Nos. 6, 7, 10 and 12;
- SEQ ID Nos. 6, 7, 10 and 13;
- 30 • SEQ ID Nos. 6, 7, 10 and 14;
- SEQ ID Nos. 6, 7, 11 and 12;
- SEQ ID Nos. 6, 7, 11 and 13;
- SEQ ID Nos. 6, 7, 11 and 14;
- SEQ ID Nos. 6, 7, 12 and 13;
- 35 • SEQ ID Nos. 6, 7, 12 and 14;
- SEQ ID Nos. 6, 7, 13 and 14;
- SEQ ID Nos. 6, 8, 10 and 11;
- SEQ ID Nos. 6, 8, 10 and 12;

- SEQ ID Nos. 6, 8, 10 and 13;
- SEQ ID Nos. 6, 8, 10 and 14;
- SEQ ID Nos. 6, 8, 11 and 12;
- SEQ ID Nos. 6, 8, 11 and 13;
- 5 • SEQ ID Nos. 6, 8, 11 and 14;
- SEQ ID Nos. 6, 8, 12 and 13;
- SEQ ID Nos. 6, 8, 12 and 14;
- SEQ ID Nos. 6, 8, 13 and 14;
- SEQ ID Nos. 6, 9, 10 and 11;
- 10 • SEQ ID Nos. 6, 9, 10 and 12;
- SEQ ID Nos. 6, 9, 10 and 13;
- SEQ ID Nos. 6, 9, 10 and 14;
- SEQ ID Nos. 6, 9, 11 and 12;
- SEQ ID Nos. 6, 9, 11 and 13;
- 15 • SEQ ID Nos. 6, 9, 11 and 14;
- SEQ ID Nos. 6, 9, 12 and 13;
- SEQ ID Nos. 6, 9, 12 and 14;
- SEQ ID Nos. 6, 9, 13 and 14;
- SEQ ID Nos. 7, 8, 10 and 11;
- 20 • SEQ ID Nos. 7, 8, 10 and 12;
- SEQ ID Nos. 7, 8, 10 and 13;
- SEQ ID Nos. 7, 8, 10 and 14;
- SEQ ID Nos. 7, 8, 11 and 12;
- SEQ ID Nos. 7, 8, 11 and 13;
- 25 • SEQ ID Nos. 7, 8, 11 and 14;
- SEQ ID Nos. 7, 8, 12 and 13;
- SEQ ID Nos. 7, 8, 12 and 14;
- SEQ ID Nos. 7, 8, 13 and 14;
- SEQ ID Nos. 7, 9, 10 and 11;
- 30 • SEQ ID Nos. 7, 9, 10 and 12;
- SEQ ID Nos. 7, 9, 10 and 13;
- SEQ ID Nos. 7, 9, 10 and 14;
- SEQ ID Nos. 7, 9, 11 and 12;
- SEQ ID Nos. 7, 9, 11 and 13;
- 35 • SEQ ID Nos. 7, 9, 11 and 14;
- SEQ ID Nos. 7, 9, 12 and 13;
- SEQ ID Nos. 7, 9, 12 and 14;
- SEQ ID Nos. 7, 9, 13 and 14;

- SEQ ID Nos. 8, 9, 10 and 11;
- SEQ ID Nos. 8, 9, 10 and 12;
- SEQ ID Nos. 8, 9, 10 and 13;
- SEQ ID Nos. 8, 9, 10 and 14;
- 5 • SEQ ID Nos. 8, 9, 11 and 12;
- SEQ ID Nos. 8, 9, 11 and 13;
- SEQ ID Nos. 8, 9, 11 and 14;
- SEQ ID Nos. 8, 9, 12 and 13;
- SEQ ID Nos. 8, 9, 12 and 14;
- 10 • SEQ ID Nos. 8, 9, 13 and 14; or
- a variant sequence, a derivative or a salt of any of said sequences.

Embodiment 7. The composition of embodiment 6, further comprising at least one additional peptide selected from any of the peptides consisting of an amino acid sequence of SEQ ID NOs. 5 to 36 or 147, or a variant sequence, a derivative or a salt thereof.

- 15 Embodiment 8. The composition of embodiment 7, comprising one or two additional peptides.

Embodiment 9. The composition of any of the preceding embodiments, comprising at least one peptide which is a variant sequence selected from peptides having SEQ ID Nos. 37-146, wherein said variant sequence includes an overlap of at least 9 amino acid residues when aligned with a peptide of the primary pool (SEQ ID Nos. 5 to 14) or a peptide of the secondary pool (SEQ ID Nos. 20 15 to 36).

Embodiment 10. The composition of any of the preceding embodiments, comprising at least one peptide having a variant sequence selected from SEQ ID Nos. 58, 59, 66, 68, 69, 75, 76, 77, 78, 98, 107, 113, 119, 131 and 132.

- 25 Embodiment 11. The composition of any of the preceding embodiments, comprising a peptide consisting of the sequence DLKIKLRRTIEAEGIP (SEQ ID No. 147), or a variant sequence, a derivative or a salt thereof.

Embodiment 12. The composition of embodiment 1 which comprises five peptides, where said peptides consist of amino acid sequences:

- SEQ ID Nos. 5, 9, 18, 26 and 27;
- 30 • SEQ ID Nos. 7, 9, 25, 26 and 31;
- SEQ ID Nos. 9, 12, 14, 17 and 26;
- SEQ ID Nos. 9, 13, 16, 26 and 35;
- SEQ ID Nos. 8, 9, 11, 26 and 32;
- SEQ ID Nos. 7, 18, 25, 28 and 31;

- SEQ ID Nos. 5, 13, 18, 25 and 27;
- SEQ ID Nos. 10, 14, 15, 18 and 25;
- SEQ ID Nos. 8, 12, 18, 25 and 30;
- SEQ ID Nos. 6, 11, 18, 25 and 35;
- 5 • SEQ ID Nos. 5, 8, 13, 14 and 27;
- SEQ ID Nos. 5, 7, 27, 28 and 31;
- SEQ ID Nos. 5, 10, 15, 27 and 35;
- SEQ ID Nos. 5, 17, 24, 27 and 32;
- SEQ ID Nos. 5, 16, 27, 30 and 33;
- 10 • SEQ ID Nos. 7, 8, 13, 14 and 31;
- SEQ ID Nos. 7, 10, 14, 17 and 24;
- SEQ ID Nos. 7, 11, 14, 28 and 35;
- SEQ ID Nos. 7, 12, 14, 16 and 32;
- SEQ ID Nos. 7, 14, 29, 30 and 33;
- 15 • SEQ ID Nos. 8, 12, 13, 15 and 31;
- SEQ ID Nos. 8, 10, 13, 17 and 28;
- SEQ ID Nos. 8, 11, 13, 16 and 35;
- SEQ ID Nos. 6, 8, 13, 20 and 32;
- SEQ ID Nos. 8, 13, 19, 29 and 33; or
- 20 • a variant sequence, a derivative or a salt of any of said sequences.

Embodiment 13. A composition comprising a peptide combination comprising at least five different peptides, where said at least five peptides consist of amino acid sequences:

- SEQ ID Nos. 106, 63, 77, 112 and 53;
- 25 • SEQ ID Nos. 106, 63, 87, 56 and 85;
- SEQ ID Nos. 106, 63, 100, 49 and 124;
- SEQ ID Nos. 106, 63, 113, 62 and 123;
- SEQ ID Nos. 106, 63, 107, 59 and 68;
- SEQ ID Nos. 100, 77, 53, 123 and 85;
- 30 • SEQ ID Nos. 100, 77, 119, 49 and 124;
- SEQ ID Nos. 100, 77, 110, 48 and 84;
- SEQ ID Nos. 100, 77, 97, 107 and 73;
- SEQ ID Nos. 100, 77, 98, 59 and 129;
- SEQ ID Nos. 112, 53, 123, 56 and 95;
- 35 • SEQ ID Nos. 112, 53, 124, 85 and 62;
- SEQ ID Nos. 112, 53, 107, 87 and 81;
- SEQ ID Nos. 112, 53, 84, 97 and 59;

- SEQ ID Nos. 112, 53, 119, 52 and 48;
- SEQ ID Nos. 87, 49, 85, 48 and 123;
- SEQ ID Nos. 87, 49, 119, 62 and 56;
- SEQ ID Nos. 87, 49, 107, 97 and 73;
- 5 • SEQ ID Nos. 87, 49, 124, 129 and 95;
- SEQ ID Nos. 87, 49, 110, 84 and 58;
- SEQ ID Nos. 123, 119, 48, 95 and 56;
- SEQ ID Nos. 123, 119, 73, 62 and 107;
- SEQ ID Nos. 123, 119, 58, 125 and 52;
- 10 • SEQ ID Nos. 123, 119, 81, 59 and 85;
- SEQ ID Nos. 123, 119, 82, 64 and 84;
- SEQ ID Nos. 107, 48, 124, 95 and 85;
- SEQ ID Nos. 107, 48, 97, 56 and 125;
- SEQ ID Nos. 107, 48, 110, 62 and 59;
- 15 • SEQ ID Nos. 107, 48, 132, 129 and 52; or
- a variant sequence, a derivative or a salt of any of said sequences.

Embodiment 14. A pharmaceutical composition comprising a composition according to any of embodiments 1 to 13.

Embodiment 15. A kit comprising a compartment and instructions,

- 20 A) wherein the compartment comprises a composition according to any one of
embodiments 1 to 13, and
- B) wherein the instructions are for use in treating allergy to Japanese cedar pollen.

Embodiment 16. A method for treating allergy to Japanese cedar pollen in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a

- 25 composition according to any of embodiments 1 to 13.

Embodiment 17. The method of embodiment 16, wherein the composition further is effective for treatment of allergy to pollen that is cross-reactive with Japanese cedar pollen, e.g. pollen from members of the Cupressaceae family.

Embodiment 18. A composition according to any of embodiments 1 to 13 for use in the treatment

- 30 of allergy to Japanese cedar pollen in a subject in need thereof.

Embodiment 19. The composition of embodiment 18, wherein the composition further is for use in the treatment of allergy to pollen that is cross-reactive with Japanese cedar pollen, e.g. pollen from members of the Cupressaceae family.

Embodiment 20. Use of a composition according to any of embodiments 1 to 13 for the preparation of a medicament for the treatment of allergy to Japanese cedar pollen in a subject in need thereof.

Embodiment 21. Use according to embodiment 20, wherein the medicament is also for treatment of allergy to pollen that is cross-reactive with Japanese cedar pollen, e.g. pollen from members of the Cupressaceae family.

Embodiment 22. An *in vitro* method of determining whether T cells of a subject in need of treatment recognize a composition as defined in any one of embodiments 1 to 13, comprising contacting said T cells obtained from the subject with said peptide combination or single peptides thereof and detecting whether said T cells are stimulated by said peptide.

Embodiment 23. The method according to claim 22, which is carried out to determine whether a subject has, or is at risk of developing, an allergy to Japanese cedar pollen.

The application further relates to the following embodiments B1 to B134:

1. A composition comprising three peptides, which independently are 13 to 25 amino acid residues in length, wherein a first peptide is selected from group a) comprising peptides of either formula I or I*, a second peptide is selected from group b) comprising peptides of either formula II or II* and a third peptide is selected from group c) comprising peptides of group a) and b), wherein

- a peptide of formula I has an amino acid sequence defined by: a-A1-C1-B1-b
- a peptide of formula I* has an amino acid sequence defined by: a-A1-C1*-B1-b
- a peptide of formula II has an amino acid sequence defined by: a-A2-C2-B2-b
- a peptide of formula II* has an amino acid sequence defined by: a-A2-C2*-B2-b

and wherein

- C1 is an amino acid sequence selected from any one of SEQ ID NOs: 77, 48, 56 and 66,
- C1* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C1 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C1* is shorter than C1;
- C2 is an amino acid sequence selected from any one of SEQ ID NOs: 97, 107 and 125;
- C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C2* is shorter than C2;
- A1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;

- B1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
 - A2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
 - 5 - B2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
 - a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);
- 10 and wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.
2. The compositions according to embodiment 1, wherein the only substitution(s) in C1*, C2*, A1, A2, B1 and B2 is cysteine substituted with serine.
- 15 3. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein
- C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,
 C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or SEQ ID
 20 NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions, and
- a second peptide selected from peptides of formula II and II*, wherein
- C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,
 C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID
 25 NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,
- wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.
4. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein
- 30 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,
 C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or SEQ ID NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions.

5. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 48 or 77 with 0, 1, or 2 amino acid

5 substitutions compared to a fragment SEQ ID NOs: 48 or 77 of the same length, or SEQ ID NOs: 48 or 77 with 1 or 2 amino acid substitutions.

6. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77,

10 C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions.

7. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein

15 C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions.

8. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein

20

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions.

9. The composition according to any one of the preceding embodiments comprising a first peptide selected from peptides of formula I and I*, wherein

25

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions.

30

10. The composition according to any one of the preceding, wherein the first peptide as defined in any one of the embodiments 4 to 9 is of formula I.

11. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

5 C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125, C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions.

10 12. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97 and 107, C2* in formula II* is either a fragment of SEQ ID NOs: 97 or 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97 or 107 of the same length, or SEQ ID NOs: 97 or 107 with 1 or 2 amino acid substitutions.

15 13. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97 and 125, C2* in formula II* is either a fragment of SEQ ID NOs: 97 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97 or 125 of the same length, or SEQ ID NOs: 20 97 or 125 with 1 or 2 amino acid substitutions.

14. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97, C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions. 25

15. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107, 30 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO:107 with 1 or 2 amino acid substitutions.

16. The composition according to any one of the preceding embodiments comprising a second peptide selected from peptides of formula II and II*, wherein

5 C2 in formula II is an amino acid sequence of SEQ ID NO: 125,
C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO:125 with 1 or 2 amino acid substitutions.

10 17. The composition according to any one of the preceding embodiments, wherein the second peptide as defined in any one of the embodiments 0 to 0 is of formula II.

18. The composition according to any one of the preceding embodiments comprising a third peptide selected from peptides of formula I, II, I* and II*, wherein

15 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56 or 77 of the same length, or SEQ ID NOs: 48, 56 or 77 with 1 or 2 amino acid substitutions,

20 C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,
C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

19. The composition according to any one of the preceding embodiments comprising a third peptide selected from peptides of formula I, II, I* and II*, wherein

25 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48 and 77,
C1* in formula I* is either a fragment of SEQ ID NOs: 48 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48 or 77 of the same length, or SEQ ID NOs: 48 or 77 with 1 or 2 amino acid substitutions,

30 C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,
C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

- 5 20. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

- 10 C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 15 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

- 20 C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

21. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

- 25 C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

5 a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

10 wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

22. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

15 C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

20 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

25 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions;

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

30 23. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

5 a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions, and

10 a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

15 wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

24. The composition according to any one of the preceding embodiments, comprising three peptides having an amino acid sequence as defined for peptide mixes numbered 242, 242a, 243, 243a, 243b, 273, 273a, 273b, 240, 240a, 246, 246a, 246b, 236, 236a, 236b, 238, 238a, 238b, 238c, 238d, 241, 241a, 241b, 245 and 244 in Table 7a.

20

25. The composition according to any one of the preceding embodiments comprising a fourth, fifth, sixth and/or further peptide independently selected from peptides of formula I, II, I* and II*, wherein

25 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 49, 56, 59, 64, 66 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 of the same length, or SEQ ID NOs: 48, 49, 56, 59, 64, 66 or 77 with 1 or 2 amino acid substitutions,

30 C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 98, 100, 107, 113 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 98, 100, 107, 113 or 125 with 0, 1, or 2

amino acid substitutions compared to a fragment SEQ ID NOs: 97, 98, 100, 107, 113 or 125 of the same length, or SEQ ID NOs: 97, 98, 100, 107, 113 or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

- 5 26. The composition according to any one of the preceding embodiments comprising a fourth, fifth, sixth and/or further peptide independently selected from peptides of formula I, II, I* and II*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 48, 56, 66 and 77,

- 10 C1* in formula I* is either a fragment of SEQ ID NOs: 48, 56, 66 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 48, 56, 66 or 77 of the same length, or SEQ ID NOs: 48, 56, 66 or 77 with 1 or 2 amino acid substitutions,

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107, and 125,

- 15 C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107, or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107, or 125 of the same length, or SEQ ID NOs: 97, 107, or 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

27. The composition according to any one of the preceding embodiments, comprising four peptides as defined in any one of the peptide mixes numbered 253, 253a, 253b, 247, 247a, 247b, 20 293, 293a, 293b, 293c, 293d, 251, 251a, 251b, 248, 248a, 248b, 248c, 248d, 252, 252a, 252b, 252c, 252d, 254, 250, 255 and 249 in Table 8a.

28. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

- 25 C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 30 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

- 5 C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO:107 with 1 or 2 amino acid substitutions;

a fourth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

- 10 C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO:125 with 1 or 2 amino acid substitutions; and

a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

- 15 C1* in formula II* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

- 20 29. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

- 25 C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 30 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO:107 with 1 or 2 amino acid substitutions;

a fourth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO:125 with 1 or 2 amino acid substitutions; and

a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 66,

C1* in formula I* is either a fragment of SEQ ID NO: 66 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 66 of the same length, or SEQ ID NO: 66 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

30. The composition according to any one of the preceding embodiments, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO:107 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions;

5 a fourth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,

C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48 with 1 or 2 amino acid substitutions; and

10 a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,

C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

15 wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

31. The composition according to any one of the preceding embodiments, comprising five peptides as defined in any one of the peptide mixes numbered 153, 153a, 153b, 256, 256a, 256b, 259, 259a, 259b, 259c, 259d, 261, 261a, 261b, 261c and 261d as shown in Table 9a.

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32. The composition according to any one of the preceding embodiments, comprising a sixth peptide selected from peptides of formula I or formula I*, wherein C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 77 and 66,

C1* in formula I* is either a fragment of SEQ ID NOs: 77 or 66 with 0, 1, or 2 amino acid

25 substitutions compared to a fragment SEQ ID NOs: 77 or 66 of the same length, or SEQ ID NOs: 77 or 66 with 1 or 2 amino acid substitutions.

33. The composition according to any one of the preceding embodiments, comprising a sixth peptide selected from peptides of formula I or formula I*, wherein C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 77 and 56,

30

C1* in formula I* is either a fragment of SEQ ID NOs: 77 or 56 with 0, 1, or 2 amino acid

substitutions compared to a fragment SEQ ID NOs: 77 or 56 of the same length, or SEQ ID NOs: 77 or 56 with 1 or 2 amino acid substitutions.

34. The composition according to any one of the preceding embodiments, comprising a sixth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

- 5 C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions.

35. The composition according to any one of the preceding embodiments, comprising six peptides as defined in any one of the peptide mixes numbered 263, 263a, 263b, 267, 267a, 267b,
10 267c, 267d, 264, 264a, 264b, 264c, 264d, 265, 265a, 265b, 265c, 265d, 262, 262a, 262b, 262c and 262d shown in Table 10a.

36. The composition according to any one of embodiments 1 to 34, comprising:

a first peptide having the amino acid sequence of:

- 15 a) SEQ ID NO: 48 or SEQ ID NO:148,
b) SEQ ID NO: 56 or SEQ ID NOs: 154, 155, 156 or 157,
c) SEQ ID NO: 66 or SEQ ID NOs: 170, 166, 167 or 6, or
d) SEQ ID NO: 77 or SEQ ID NO: 176.

37. The composition according to any one of embodiments 1 to 36 comprising:

20 the second peptide having the amino acid sequence of:

- e) SEQ ID NO: 97 or SEQ ID NO:184,
f) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195, or
g) SEQ ID NO: 125 or SEQ ID NO: 208.

38. The composition according to any one of the embodiments 36 and 37 comprising a third
25 peptide having the same amino acid sequence as a peptide defined in a) to d) in embodiment 36 or e) to g) in embodiment 37, and not selected from the same a) to g) as any other peptide in the composition.

39. The composition according to any one of the preceding embodiments comprising a fourth peptide having the same amino acid sequence as a peptide defined in a) to d) in

embodiment 36 or e) to g) in embodiment 37, and not selected from the same a) to g) as any other peptide in the composition.

40. The composition according to any one of the preceding embodiments comprising a fifth peptide having the same amino acid sequence as a peptide defined in a) to d) in embodiment 36 or e) to g) in embodiment 37, and not selected from the same a) to g) as any other peptide in the composition.

41. The composition according to any one of the preceding embodiments comprising a sixth peptide having the same amino acid sequence as a peptide defined in a) to d) in embodiment 36 or e) to g) in embodiment 37, and not selected from the same a) to g) as any other peptide in the composition.

42. A composition comprising three peptides, which independently are 13 to 25 amino acid residues in length, said composition comprising:

a first peptide having the amino acid sequence of:

- a) SEQ ID NO: 48 or SEQ ID NO:148,
- b) SEQ ID NO: 56 or SEQ ID NOs: 154, 155, 156 or 157,
- c) SEQ ID NO: 66 or SEQ ID NOs: 170, 166, 167 or 6,
- d) SEQ ID NO: 77 or SEQ ID NOs: 176;

a second peptide having the amino acid sequence of:

- e) SEQ ID NO: 97 or SEQ ID NO:184,
- f) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195,
- g) SEQ ID NO: 125 or SEQ ID NOs: 208; and

a third peptide having the same amino acid sequence as a peptide defined in a) to g), and not selected from the same a) to g) as any other peptide in the composition.

43. The composition according to embodiment 42 comprising:

a first peptide having the amino acid sequence of:

- h) SEQ ID NO: 48 or SEQ ID NO:148,
- i) SEQ ID NO: 77 or SEQ ID NO: 176; and/or

a second peptide having the amino acid sequence of:

- j) SEQ ID NO: 97 or SEQ ID NO:184,
- k) SEQ ID NO: 107 or SEQ ID NOs: 11, 194 or 195,
- l) SEQ ID NO: 125 or SEQ ID NOs: 208; and/or

- 5 a third peptide having the same amino acid sequence as a peptide defined in h) to l), and not selected from the same h) to l) as any other peptide in the composition.

44. The composition according to embodiment 42, comprising:

a first peptide having the amino acid sequence of:

- m) SEQ ID NO:148,
- 10 n) SEQ ID NOs: 155 or 157,
- o) SEQ ID NOs: 170 or 167, or
- p) SEQ ID NO: 176; and/or

the second peptide having the amino acid sequence of:

- q) SEQ ID NO:184,
- 15 r) SEQ ID NOs: 194 or 195, or
- s) SEQ ID NO: 208; and/or

the third peptide having the same amino acid sequence as a peptide defined above in m) to s), and not selected from the same m) to s) as any other peptide in the composition.

45. The composition according to embodiment 42 comprising:

- 20 a first peptide having the amino acid sequence of:

- t) SEQ ID NO:148,
- u) SEQ ID NO: 176; and/or

a second peptide having the amino acid sequence of:

- v) SEQ ID NO:184,

w) SEQ ID NOs: 194 or 195,

x) SEQ ID NO: 208; and/or

a third peptide having the same amino acid sequence as a peptide defined in t) to x), and not selected from the same t) to x) as any other peptide in the composition.

5 46. The composition according to any one of the embodiments 42 to 45 comprising a fourth, fifth and/or sixth peptide independently having the same amino acid sequence as a peptide selected from a) to g) of embodiment 42, each not having the same definition a) to g) as another peptide in the composition.

10 47. The composition according to any one of the embodiments 42 to 46 comprising a fourth, fifth and/or sixth peptide independently having the same amino acid sequence as a peptide selected from h) to l) of embodiment 43, each not having the same definition h) to l) as another peptide in the composition.

15 48. The composition according to any one of the embodiments 42 to 47 comprising a further peptide independently having the same amino acid sequence as a peptide selected from a) to g) of embodiment 42 or from h) to l) of embodiment 43, each not having the same definition a) to l) as another peptide in the composition.

20 49. The composition according to any one of the preceding embodiments comprising a fourth, fifth, sixth and/or further peptide, which peptide(s) independently are 13 to 25 amino acid residues in length, wherein any one of the fourth, fifth, sixth or further peptide is of either formula III or III* or formula IV or IV*, wherein

- a peptide of formula III has an amino acid sequence defined by: a-A3-C3-B3-b
- a peptide of formula III* has an amino acid sequence defined by: a-A3-C3*-B3-b
- a peptide of formula IV has an amino acid sequence defined by: a-A4-C4-B4-b
- a peptide of formula IV* has an amino acid sequence defined by: a-A4-C4*-B4-b

25

and wherein

- C3 is an amino acid sequence selected from any one of SEQ ID NOs: 49, 59, or 64,
 - C3*consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C3 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C3* is shorter than C3;
 - C4 is an amino acid sequence selected from any one of SEQ ID NOs: 14, 98, 100 or 113,
 - C4*consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C4 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C4* is shorter than C4;
- 30

- A3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- B3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- 5 - A4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- B4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

and wherein C3, C3*, C4, or C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO as C1, C1*, C2, C2*, C3 or C3* or C4 or C4* as any other peptide in the composition.

15

50. The compositions according to embodiment 49, wherein the only substitution(s) in C3*, C4*, A3, A4, B3 and B4 is cysteine substituted with serine.

51. The composition according to any one of embodiments 49 to 50, wherein a peptide is selected from peptides of formula III, III*, IV and IV*,

20 wherein C3 in formula III is an amino acid sequence of SEQ ID NO: 49,

C3* in formula III* is either a fragment of SEQ ID NO: 49 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 49 of the same length, or SEQ ID NO: 49 with 1 or 2 amino acid substitutions;

25 wherein C4 in formula IV is an amino acid sequence selected from any one of SEQ ID NOs: 98 and 100, C4* in formula IV* is either a fragment of SEQ ID NOs: 98 or 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 98 or 100 of the same length, or SEQ ID NOs: 98 or 100 with 1 or 2 amino acid substitutions.

52. The composition according to any one of embodiments 49 to 51 comprising a first peptide selected from peptides of formula I and I*, wherein

30 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77, C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions, and

a third peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56 and 77,

C1* in formula I* is either a fragment of SEQ ID NOs: 56 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 56 or 77 of the same length, or SEQ ID NOs: 56 or 77 with 1 or 2 amino acid substitutions, and peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence selected from SEQ ID NOs: 97, 107 and 125,

C2* in formula II* is either a fragment of SEQ ID NOs: 97, 107 or 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NOs: 97, 107 or 125 of the same length, or SEQ ID NOs: 97, 107 or 125 with 1 or 2 amino acid substitutions

wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

53. The composition according to any one of embodiments 49 to 51 comprising

a first peptide of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 77,

C1* in formula I* is either a fragment of SEQ ID NO: 77 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 77 of the same length, or SEQ ID NO: 77 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,

C2* in formula II* is of SEQ ID NO: 97 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,

C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions

compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions,

a fourth peptide selected from peptides of formula IV and IV*, wherein

5 C4 in formula IV is an amino acid sequence of SEQ ID NO: 100, C4* in formula IV* is either a fragment of SEQ ID NO: 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 100 of the same length, or SEQ ID NO: 100 with 1 or 2 amino acid substitutions, and

a fifth peptide selected from peptides of formula I and I*, wherein

10 C1 in formula I is an amino acid sequence of SEQ ID NO: 56, C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, C2*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C4 as any other peptide in the composition.

15 54. The composition according to any one of embodiments 49 to 53, comprising five peptides as defined in any one of the peptide mixes numbered 313, 313a, 313b and 313c shown in Table 11a.

55. The composition according to any one of embodiments 49 to 54 comprising

a first peptide of formula I and I*, wherein

20 C1 in formula I is an amino acid sequence of SEQ ID NO: 56, C1* in formula I* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

25 C2 in formula II is an amino acid sequence of SEQ ID NO: 107, C2* in formula II* is of SEQ ID NO: 107 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,

C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125 with 1 or 2 amino acid substitutions,

- 5 a fourth peptide selected from peptides of formula IV and IV*, wherein

wherein C4 in formula IV is an amino acid sequence of SEQ ID NO: 100, C4* in formula IV* is either a fragment of SEQ ID NO: 100 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 100 of the same length, or SEQ ID NO: 100 with 1 or 2 amino acid substitutions, and

- 10 a fifth peptide selected from peptides of formula III and III*, wherein

wherein C3 in formula III is an amino acid sequence of SEQ ID NO: 49, C3* in formula III* is either a fragment of SEQ ID NO: 49 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 49 of the same length, or SEQ ID NO: 49 with 1 or 2 amino acid substitutions,

- 15 wherein C1, C1*, C2, C2*, C3, C3*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C3, C4 as any other peptide in the composition.

56. The composition according to embodiment 55, comprising five peptides as defined in any one of the peptide mixes numbered 315, 315a, 315b, 315c, 315d, 315e and 315f shown in Table 11a.

- 20 57. The composition according to embodiment 55 further comprising a sixth peptide selected from peptides of formula IV and IV*, wherein

wherein C4 in formula IV is an amino acid sequence of SEQ ID NO: 98, C4* in formula IV* is either a fragment of SEQ ID NO: 98 with 0, 1, or 2 amino acid substitutions compared to a fragment SEQ ID NO: 98 of the same length, or SEQ ID NO: 98 with 1 or 2 amino acid substitutions,

- 25 wherein C1, C1*, C2, C2*, C3, C3*, C4, C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1, C2, C3, C4 as any other peptide in the composition.

58. The composition according to embodiment 57, comprising six peptides as defined in any one of the peptide mixes numbered 335, 335a, 335b, 335c, 335d, 335e and 335f shown in Table 11a.
- 30

59. The composition according to any one of the preceding embodiments, comprising three or at least three peptides having the amino acid sequences as defined for peptide mixes numbered 242, 242a, 243, 243a, 243b, 273, 273a, 273b, 240, 240a, 246, 246a, 246b, 236, 236a, 236b, 238, 238a, 238b, 238c, 238d, 241, 241a, 241b, 245 and 244 in Table 7a.

5 60. The composition according to any one of the preceding embodiments comprising four or at least four peptides having the amino acid sequences as defined for peptide mixes numbered 253, 253a, 253b, 247, 247a, 247b, 293, 293a, 293b, 293c, 293d, 251, 251a, 251b, 248, 248a, 248b, 248c, 248d, 252, 252a, 252b, 252c, 252d, 254, 250, 255 and 249 in Table 8a.

10 61. The composition according to any one of the preceding embodiments comprising five or at least five peptides having the amino acid sequences as defined for peptide mixes numbered 153, 153a, 153b, 256, 256a, 256b, 259, 259a, 259b, 259c, 259d, 261, 261a, 261b, 261c and 261d as shown in Table 9a.

15 62. The composition according to any one of the preceding embodiments comprising six or at least six peptides having the amino acid sequences as defined for peptide mixes numbered 263, 263a, 263b, 267, 267a, 267b, 267c, 267d, 264, 264a, 264b, 264c, 264d, 265, 265a, 265b, 265c, 265d, 262, 262a, 262b, 262c and 262d shown in Table 10a.

20 63. The composition according to any one of the preceding embodiments comprising three, four, five or six peptides having the amino acid sequences as defined for peptide mixes numbered 282, 277, 281, 297, 301, 302, 295, 299, 316, 320, 313, 313a, 313b, 313c, 315, 315a, 315b, 315c, 315d, 315e, 315f, 335, 336, 340, 335a, 335b, 335c, 335d, 335e and 335f of Table 11a.

64. The composition according to any one of the preceding embodiments comprising at least 4, 5, 6, 7 or 8 peptides.

25 65. The composition according to any one of the preceding embodiments comprising at the most 4, 5, 6, 7 or 8 peptides.

66. The composition according to any one of the preceding embodiments, wherein the C1, C1*, C2, or C2* in the third peptide binds at least one additional HLA Class II molecule than is bound by the C1 or C1* in the first peptide and the C2 or C2* found in the second peptide.

30 67. The composition according to any one of the preceding embodiments, comprising a fourth, fifth and/or sixth peptide selected from the group of peptides c) in embodiment 1 and wherein C1, C1*, C2, or C2* in any of the fourth, fifth or sixth peptide is not identical to, or defined from, the same SEQ ID NO of any one of the other peptides of the composition.

68. The composition according to any one of the preceding embodiments, comprising a fourth, fifth and/or sixth peptide selected from the group of peptides c) in embodiment 1, and wherein C1, C1*, C2, or C2* in each of the fourth, fifth or sixth peptide binds at least one additional HLA Class II molecule than is bound by the C1, C1*, C2, or C2* present in any one of the other peptides in the composition.

69. The composition according to any one of the preceding embodiments, comprising a fourth, fifth and/or sixth peptide selected from formula III, III*, IV or IV*, and wherein C3, C3*, C4, or C4* in each of the fourth, fifth or sixth peptide binds at least one additional HLA Class II molecule than is bound by the C1, C1*, C2, or C2* present in any one of the other peptides in the composition.

70. The composition according to any one of the preceding embodiments, wherein at least one of the amino acid substitutions in C1*, C2*, A1, B1, A2 and B2 is the substitution of a cysteine amino acid residue by a serine amino acid residue or by a 2-aminobutyric acid amino acid residue.

71. The composition according to any one of the preceding embodiments wherein at least one of the amino acid substitutions in C1*, C2*, A1, B1, A2 and B2 is the substitution of a cysteine amino acid residue by a serine amino acid residue.

72. The composition according to any one of the preceding embodiments, wherein any cysteine amino acid residue in any of the peptides of the composition is substituted by a serine amino acid residue or by a 2-aminobutyric acid amino acid residue.

73. The composition according to any one of the preceding embodiments, wherein any cysteine amino acid residue in any of the peptides of the composition is substituted by a serine amino acid residue.

74. The composition according to any one of the preceding embodiments, wherein the peptides of the composition in combination bind at least 18 of 26 HLA Class II molecules selected from the group consisting of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101, DRB5_0101, such as at least 19, 20, 21, 22, 23, 24, 25 or 27 of said HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

75. The composition according to any one of the preceding embodiments, wherein the peptides of the composition in combination bind at least 70% of the HLA Class II molecules of Table

5, column 3, such as at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

76. The composition according to any one of the preceding embodiments, wherein any of the amino acid sequences of the C1* and C2* in the composition binds at least 70% of the HLA Class II molecules that C1 and C2 binds, respectively, such as binds at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that C1 and C2 binds, respectively, when binding is determined by similar in vitro or in silico test conditions.

77. The composition according to any one of the preceding embodiments, wherein any of the amino acid sequence(s) of a peptide of formula I or I* binds at least 70% of the HLA Class II molecules that the respective C1 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C1 binds, when binding is determined by similar in vitro or in silico test conditions.

78. The composition according to any one of the preceding embodiments, wherein the amino acid sequence of a peptide(s) of formula II or II* binds at least 70% of the HLA Class II molecules that the respective C2 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C2 binds, when binding is determined by similar in vitro or in silico test conditions.

79. The composition according to any one of the preceding embodiments, wherein the amino acid sequence of a peptide(s) of formula III or III* binds at least 70% of the HLA Class II molecules that the respective C3 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C3 binds, when binding is determined by similar in vitro or in silico test conditions.

80. The composition according to any one of the preceding embodiments, wherein the amino acid sequence of a peptide(s) of formula IV or IV* binds at least 70% of the HLA Class II molecules that the respective C4 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C4 binds, when binding is determined by similar in vitro or in silico test conditions.

81. The composition according to any one of the preceding embodiments, wherein the group of HLA Class II molecules consists of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101 and DRB5_0101.

82. The composition according to any one of the preceding embodiments, wherein the group of HLA Class II molecules consists of the HLA Class II molecules shown in Table 5 column 2 or 3.

83. The composition according to any one of the preceding embodiments, wherein any peptide of the composition elicits, stimulates or induces an in vitro T cell proliferation response or an in vitro IL-5 cytokine response of T cells or PBMC's obtained from an individual allergic or sensitized to cedar pollen.

84. The composition according to any one of the preceding embodiments, wherein any peptide of the composition elicits, stimulates or induces an in vitro T cell proliferation response or an in vitro IL-5 cytokine response of T cells or PBMC's obtained from an individual allergic or sensitized to a cedar pollen allergen selected from Cry j 1 and Cry j 2.

85. The composition according to any one of the preceding embodiments, wherein the 13 to 16 contiguous amino acid residues of the C1* and C2* are independently selected from 14 to 16 contiguous amino acid residues of the C1* and C2*, 15 to 16 contiguous amino acid residues of the C1* and C2* and 16 contiguous amino acid residues of the C1* and C2*.

86. The composition according to any one of the preceding embodiments, wherein the 0-6 contiguous amino acid residues of A1, B1, A2 and B2 are independently selected from 0-5 contiguous amino acid residues of A1, B1, A2 and B2, 0-4 contiguous amino acid residues of A1, B1, A2 and B2, 0-3 contiguous amino acid residues of A1, B1, A2 and B2, 0-2 contiguous amino acid residues of A1, B1, A2 and B2, 0-1 contiguous amino acid residues of A1, B1, A2 and B2, such as 0 contiguous amino acid residues of A1, B1, A2 and B2.

87. The composition according to any one of the preceding embodiments, wherein the number of amino acid residue substitutions of the C1* and C2* are independently selected from 0, 1 or 2.

88. The composition according to any one of the preceding embodiments, wherein the number of amino acid residue substitutions of the A1, B1, A2 and B2 are independently selected from 0 or 1.

89. The composition according to any one of the preceding embodiments, wherein the total number of amino acid residues in the A1 and B1 of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

90. The composition according to any one of the preceding embodiments, wherein the total number of amino acid residues in A2 and B2 of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

91. The composition according to any one of the preceding embodiments, wherein the total number of amino acid residues in the a, A1, B1 and b of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
92. The composition according to any one of the preceding embodiments, wherein the total number of amino acid residues in the a, A2, B2 and b of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
93. The composition according to any one of the preceding embodiments, wherein the amino acid residues of a and b independently is 0, 1 or 2 lysine (K).
94. The composition according to any one of the preceding embodiments, wherein the amino acid residues of a and b independently is 0, 1 or 2 arginine (R).
95. The composition according to any one of the preceding embodiments, wherein the amino acid residues of a and b independently is 0, 1 or 2 aspartic acid (D).
96. The composition according to any one of the preceding embodiments, wherein the amino acid residues of a and b in total is 0, 1, 2 or 3 amino residues.
97. The composition according to any one of the preceding embodiments, wherein the length of the peptides each is independently selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25 amino acid residues in length.
98. The composition according to any one of the preceding embodiments, wherein a peptide of formulas I, I*, II and II* comprises one or more of the modifications selected from the following:
- a) N-terminal acetylation or methylation
 - b) C terminal amidation
 - c) C-terminal amination
 - d) replacement of one or more hydrogen on the side chain amines of arginine and/or lysine with a methylene group
 - e) glycosylation, and
 - f) phosphorylation.
99. The composition according to any one of the preceding embodiments, wherein any one of the peptides in the composition is a salt .
100. The composition according to any one of the preceding embodiments, wherein the peptides of the composition are obtained synthetically or by recombinant expression.

101. The composition according to any one of the preceding embodiments, wherein the peptides are freeze-dried, such as in a freeze-dried state.

102. The composition according to any one of the preceding embodiments, wherein each peptide in the composition is present in a molar concentration of 1 to 1000 μM , preferably 1-100 μM and more preferred in 1-10 μM .

103. The composition according to any one of the preceding embodiments, wherein each peptide in the composition is present in a soluble form in a molar concentration of 1 to 1000 μM preferably 1-100 μM and more preferred in 1-10 μM .

104. The composition according to any one of the preceding embodiments, wherein each peptide in the composition is present in equimolar concentrations or in substantially equimolar concentrations.

105. A pharmaceutical composition comprising a composition according to any of embodiments 1 to 104.

106. The pharmaceutical composition according to embodiment 105, further comprising a pharmaceutically acceptable carrier, excipient and/or adjuvant, optionally sterile.

107. The pharmaceutical composition according to any one of embodiments 105 and 106 formulated as a vaccine for parenteral administration.

108. The pharmaceutical composition according to any one of embodiments 105 to 107, wherein the pharmaceutical composition is a powder.

109. The pharmaceutical composition according to any one of embodiments 105 to 108, wherein the composition is formulated to be re-dissolved before use.

110. The pharmaceutical composition according to any one of embodiments 105 to 109, wherein the composition is isotonic.

111. A kit comprising a compartment and instructions, wherein the compartment comprises a composition according to any one of embodiments 105 to 110, and wherein the instructions are for use in treating allergy to Japanese cedar pollen (insert latin name as well in description) or pollen having cross reactivity to Japanese cedar pollen, e.g. pollen from members of the Cupressaceae family (insert specific examples).

112. A method for treating allergy to Japanese cedar pollen, an allergen of Japanese cedar pollen, pollen cross-reactive with Japanese cedar pollen or an allergen cross reacting with an allergen of Japanese cedar pollen in a subject in need thereof, comprising administering to said

subject a therapeutically effective amount of a composition according to any of embodiments 1 to 104, a pharmaceutical composition according to any one of embodiments 105 to 110 or a kit according to embodiment 111.

113. A method for treating allergy in a subject in need thereof, where signs and/or symptoms of said allergy are elicited by exposure to Japanese cedar pollen, an allergen of Japanese cedar pollen, pollen cross-reactive with Japanese cedar pollen or an allergen cross reacting with an allergen of Japanese cedar pollen, comprising administering to said subject a therapeutically effective amount of a composition according to any of embodiments 1 to 104, a pharmaceutical composition according to any one of embodiments 105 to 110 or a kit according to embodiment 111.

114. The method according to any one of embodiments 112 and 113, wherein treating the allergy comprises or consists of relieving or reducing an immune response triggered by exposure to said Japanese cedar pollen, said allergen of Japanese cedar pollen, said pollen having cross reactivity to Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

115. The method according to any one of embodiments 112 and 113, wherein treating the allergy comprises or consists of relieving one or more symptoms of an immune response triggered by exposure to said said Japanese cedar pollen, said allergen of Japanese cedar pollen, said pollen having cross reactivity to Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

116. The method according to any one of embodiments 112 and 113, wherein treating the allergy consists of or comprises inducing immunological tolerance against said said Japanese cedar pollen, said allergen of Japanese cedar pollen, said pollen having cross reactivity to Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

117. The method according to any one of embodiments 112 to 116, wherein treating the allergy comprises or consists of relieving one or more symptom(s) associated with allergic rhinitis and/or allergic conjunctivitis and/or allergic asthma and/or allergic eczema (e.g. atopic dermatitis).

118. The method according to any one of embodiments 112 to 116, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic rhinitis, such as

- reducing the intensity of itchy nose and/or
- reducing the number of sneezes within a given period (e.g. daily, weekly, monthly) and/or
- reducing the intensity of blocked nose (congestion) and/or
- reducing the amount of nasal fluid and/or

- reducing the eosinophilic count in nasal fluid and/or
- reducing specific IgE antibody level (titre) in nasal fluid or in serum and/or
- reducing basophil histamine release of blood.

119. The method according to any one of embodiments 112 to 116, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic conjunctivitis, such as

- reducing the intensity of itchy eyes, redness in the white of the eyes and/or watery eyes; and/or
- reducing the eosinophilic count in conjunctival tissue scrapings; and/or
- reducing specific IgE antibody level (titer) in conjunctival tissue scrapings or in serum; and/or
- reducing basophil histamine release in blood.

120. The method according to any one of embodiments 112 to 116, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic asthma, such as

- reducing the intensity and/or number of coughs within a given period (e.g. daily, weekly, monthly); and/or
- reducing the intensity of wheezes; and/or
- improving being short of breath; and/or
- improving lung function; and/or
- reducing specific IgE antibody level (titre) in lung fluid or in serum; and/or
- reducing basophil histamine release in blood.

121. The method according to any one of embodiments 112 to 116, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with atopic dermatitis, such as

- reducing itch intensity of the skin; and/or
- reducing eczema score; and/or
- reducing number of (peripheral) blood eosinophils.

122. The method according to any one of embodiments 112 to 121, comprising or consisting of reducing the patient's need for concomitant treatment with corticosteroids or H1 antihistamines to reduce, relieve or suppress one or more symptoms of an immune response associated with the allergy.

123. The method according to any one of embodiments 112 to 122, wherein the immune response is clinically presented as atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anapylaxis, and/or hay fever.

124. The method according to any one of embodiments 112 to 123, wherein the method decreases, reduces, suppresses, or inhibits atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anaphylaxis, and/or hay fever.

125. The method according to any one of embodiments 112 to 124, which comprises
5 decreasing a T cell response in the patient against an allergen of Japanese cedar or a cross reacting allergen.

126. The method according to any one of embodiments 112 to 125, wherein the subject is sensitized to at least one allergen of Japanese cedar, such as to Cry j 1 and/or Cry j 2.

127. The method according to any one of embodiments 112 to 126, wherein Japanese cedar
10 pollen is pollen of the genus *Cryptomeria*, such as from the species *Cryptomeria japonica*

128. The method according to any one of embodiments 112 to 127, wherein pollen cross-reactive with Japanese cedar pollen is selected from pollen of the Cupressaceae family, such as from pollen of Japanese cypress (*Chamaecyparis obtuse*), Common cypress (*Cupressus sempervirens*) and Mountain cedar (*Juniperus ashei*).

129. The method according to any one of embodiments 112 to 127, wherein an allergen of
15 Japanese cedar pollen is Cry j 1 and/or Cry j 2.

130. The method according to any one of embodiments 112 to 129, wherein an allergen cross reacting with a Japanese cedar pollen allergen is Cha o 1 and Cha o 2.

131. A composition according to any of embodiments 1 to 0, a pharmaceutical composition
20 according to any one of the embodiments 105 to 110 or a kit according to embodiment 111 for use in the method according to any one of embodiments 112 to 130.

132. Use of a composition according to any of embodiments 1 to 0, a pharmaceutical composition according to any one of the embodiments 105 to 110 or a kit according to embodiment 111 for the preparation of a medicament for use in the method according to any one of
25 embodiments 112 to 130.

133. An in vitro method of determining whether T cells of a subject in need of treatment recognize a composition as defined in any one of embodiments 1 to 104, comprising contacting the T cells obtained from the subject with the composition or single peptide thereof and detecting whether said T cells are stimulated by the composition or peptide.

134. The method according to embodiment 133, which is carried out to determine whether a subject has, or is at risk of developing, an allergy to Japanese cedar pollen or to pollen cross reactive to Japanese cedar pollen.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described herein.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims. The invention is further exemplified by way of the following non-limited examples.

REFERENCES

Andreatta M, Karosiene E, Rasmussen M, Stryhn A, Buus S, Nielsen M. Accurate pan-specific prediction of peptide-MHC class II binding affinity with improved binding core identification. Immunogenetics, Sep 29, 2015.

Altschul, S.F., Gish, W., Miller, W., Myers, E.W. & Lipman D.J. Basic local alignment search tool, J. Mol. Biol. 215, 403-410, 1990

Bostick D, Vaisman II. A new topological method to measure protein structure similarity. Biochem Biophys Res Commun. 304, 320-325, 2003.

Greenbaum J, Sidney J, Chung J, Brander C, Peters B, Sette A. Functional classification of class II human leukocyte antigen (HLA) molecules reveals seven different supertypes and a surprising degree of repertoire sharing across supertypes. Immunogenetics, 63, 325-335, 2011.

Karosiene, Edita, Michael Rasmussen, Thomas Blicher, Ole Lund, Søren Buus, and Morten Nielsen. "NetMHCIIpan-3.0, a Common Pan-specific MHC Class II Prediction Method Including All Three Human MHC Class II Isotypes, HLA-DR, HLA-DP and HLA-DQ." Immunogenetics, Vol. 65, No. 10, 2013, p. 711-724.

McKinney DM, Southwood S, Hinz D, Oseroff C, Arlehamn CS, Schulten V, et al. A strategy to determine HLA class II restriction broadly covering the DR, DP, and DQ allelic variants most commonly expressed in the general population. *Immunogenetics*; 65:357-70, 2013.

Needleman SB, Wunsch CD. A general method applicable to the search for similarities in the amino acid sequence of two proteins, *J. Mol. Biol.* 48:443, 1970.

Oseroff C, Sidney J, Kotturi MF, Kolla R, Alam R, Broide DH, et al. Molecular determinants of T cell epitope recognition to the common Timothy grass allergen. *Journal of immunology* 2010; 185:943-55.

Pearson and Lipman, 1988: Pearson WR, Lipman DJ. Improved tools for biological sequence comparison, *Proc. Natl. Acad. Sci. USA* 85(8): 2444-2448, 1988.

Pearson WR1, Flexible sequence similarity searching with the FASTA3 program package, *Methods Mol Biol.* 132, 185-219, 2000.

Powell, M. F. and Newman M 1995 : "Compendium of vaccine adjuvants and excipients ("Vaccine Design--the subunit and adjuvant approach" (Edited by Powell, M. F. and Newman, M. J.; 1995, Pharmaceutical Biotechnology (Plenum Press, New York and London, ISBN 0-306-44867-X)

Sidney J, Southwood S, Oseroff C, del Guercio MF, Sette A, Grey HM. Measurement of MHC/peptide interactions by gel filtration. *Curr Protoc Immunol.* Chapter 18(Unit 18):13. doi: 10.1002/0471142735.im1803s31, 2001

Sidney J, Assarsson E, Moore C, Ngo S, Pinilla C, Sette A, Peters B. Quantitative peptide binding motifs for 19 human and mouse MHC class I molecules derived using positional scanning combinatorial peptide libraries. *Immunome Res.* 4:2, doi: 10.1186/1745-7580-4-2, 2008

Sidney J, Steen A, Moore C, Ngo S, Chung J, Peters B, Sette A. Divergent motifs but overlapping binding repertoires of six HLA-DQ molecules frequently expressed in the worldwide human population. *J Immunol*, 185(7), 4189-4198, 2010a.

Sidney J, Steen A, Moore C, Ngo S, Chung J, Peters B, Sette A. Five HLA-DP molecules frequently expressed in the worldwide human population share a common HLA supertypic binding specificity. *J Immunol*, 184(5), 2492-2503, 2010b.

Sidney J, Southwood S, Grey HM, Moore C, Oseroff C, Pinilla C, Sette A. Measurement of MHC/peptide interactions by gel filtration or monoclonal antibody capture. Current protocols in immunology / edited by John E. Coligan et al, Chapter 18():Unit 18.3, 2013.

- 5 Sone et al (2009): Recognition of T cell Epitope Unique to Cha 0 2, the major allergen in Japanese Cypress pollen, in allergic patients cross-reactive to Japanese Cedar and Japanese Cypress pollen, Allerg. Int. 58: 237-245,

Sone et al (1998): T cell epitopes in Japanese Cedar (Cryptomeria japonica) pollen allergens: choice of major T cell epitopes in Cry j 1 and Cry j 2 towards design of the peptide-based immunotherapeutics for the management of Japanese cedar pollinosis., J Immunol; 161:448-457

- 10 Smith and Waterman 1981: Smith and Waterman. Comparison of biosequences, Adv. Appl. Math 2: 482, 1981.

EXAMPLES

- 15 *Example 1: T-cell screening of from Cry j 1 and Cry j 2 peptides*

Table 1 below lists peptide sequences derived from the Cry j 1 and Cry j 2 proteins (SEQ ID NO: 1 and SEQ ID NO: 3), in the form of 16-mer peptides covering the entire sequence of each of the two proteins, and with eight overlapping amino acid residues between adjacent peptide sequences (SEQ ID NOs. 37-146). The peptides were screened as described below to identify useful peptides.

20

The peptides were screened for T cell reactivity in a population of Japanese cedar (JC) allergic individuals (data not shown) classified based on IgE to Japanese cedar pollen. The blood was drawn at the time of donation. All donors had lived in Japan prior to the moving to USA. Serum from these blood samples were tested for JC pollen (Cry j)-specific IgE using the ImmunoCAP system (Thermo Fischer, Uppsala, Sweden), and donors were classified as JC-sensitized or not (Cry j IgE+/ Cry j IgE-) based on a positivity threshold of >0.35 kUA/L. According to this criteria positive donors (n=10) were used to investigate peptides in T-cell assays as described below, and for selection of peptides.

25

In short, Japanese cedar-specific T-cell lines were established from peripheral blood mononuclear cells (PBMCs) of the donors, and used for testing T-cell responses following stimulation with 16-mer peptides from Cry j 1 and Cry j 2.

PBMCs were isolated from whole blood by density gradient centrifugation according to
 5 manufacturers' instructions (Ficoll-Hypaque, Amersham Biosciences, Uppsala, Sweden).

In vitro expansion of cedar-specific T cells to screen novel peptide panel: For in vitro expansion of JC-specific T cells, PBMCs were stimulated with Japanese Cedar pollen extract (ALK-Abello A/S, Horsholm, Denmark) at 2 µg/ml. Cells were cultured in RPMI 1640 supplemented with 5% human AB serum in 24 well plates (BD Biosciences, San Diego, CA) at a density of 2×10^6 /ml and
 10 incubated at 37 °C. IL-2 was added every 3 days after initial stimulation.

On day 14, cells were harvested and screened using the ELISPOT assay for reactivity against either selected peptides from Cry j 1 or Cry j 2 or peptide pools consisting of e.g. max 10 peptides. On day 17, peptides from positive pools were tested individually in ELISPOT to deconvolute the pools and identify the reactive epitopes.

15 The ELISPOT assay method: The production of IL-5 and IFN-γ from cultured PBMCs in response to stimulation with a peptide or allergen extract was measured by ELISPOT as described in Oseroff C et al., *J Immunol.* 2010; 185(2):943-55. Briefly, flat-bottom 96-well nitrocellulose plates (Millipore, Bedford, MA) were prepared according to the manufacturer's instructions and coated with 5 µg/ml of anti-human IFNγ (Clone 1-D1K; Mabtech, Cincinnati, OH) and 5 µg/ml anti-human IL-5 (clone
 20 TRFK5; Mabtech). The next day, plates were washed, blocked and cells (1×10^5 cells/well) plated with a single peptide, a peptide pool or a Japanese Cedar pollen extract (10 µg/ml, 5 µg/ml and 2 µg/ml, respectively) and incubated at 37°C. After 24 hours, cells were removed and plates incubated with biotinylated anti-human IL-5 Ab (Mabtech #3420-9H) and anti-human IFN-γ-HRP Ab (Mabtech 3490-6-1000) at 37°C. After 2 hours, plates were washed and avidin-alkaline
 25 phosphatase-complex added (Vector Laboratories, Burlingame, CA) followed by incubation for 1 h at RT. Alkaline phosphatase-conjugated spots were developed with the Vector Blue Substrate Kit (Vector Labs, Burlingame, CA). Horseradish peroxidase-conjugated spots were developed with 3-amino-9-ethylcarbazole solution (Sigma-Aldrich, St. Louis, MO). Spot-forming cells (SFC) were counted by computer-assisted image analysis (KS-ELISPOT reader, Zeiss, Munich, Germany) in
 30 each well. Positivity thresholds were 20 SFCs/ 10^6 PBMCs, $p \leq 0.05$ for stimulated cells compared to background wells without stimulation, and a stimulation index (SI) ≥ 2 . Each assay was performed in triplicate. Student's t-test, using the mean of triplicate values of stimulated cells compared to medium control, was used to calculate statistical significance. Positive pools were deconvoluted to

identify the individual T-cell epitopes.

Table 1 shows T-cell response data for overlapping 16-mer Cry j 1 and Cry j 2 peptides tested (SEQ ID NOs: 37-146). Peptides were considered positive if at least 20 % of the donors responded in accordance with the used threshold described above.

Table 1. T-cell responses and HLA coverage for Cry j 1 peptides

Cry j 1			Cry j 2		
SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)	SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)
37	MDSPCLVALLVFSFVI	20	83	MAMKLIAPMAFLAMQL	10
38	LLVFSFVIGSCFSDNP	10	84	MAFLAMQLIIMAAAED	10
39	GSCFSDNPIDSCWRGD	10	85	IIMAAAEDQSAQIMLD	10
40	IDSCWRGDSNWAQNRM	10	86	QSAQIMLDSVVEKYLR	20
41	SNWAQNRMKLADCAVG	10	87	SVVEKYLRNRSRLRKV	0
42	KLADCAVGFGSSTMGG	10	88	SNRSLRKVEHSRHDAL	10
43	FGSSTMGGKGGDLTV	10	89	EHSRHDALNIFNVEKY	0
44	KGGDLTVTNSDDDPV	10	90	NIFNVEKYGAVGDGKH	20
45	TNSDDDPVNPAPGTLR	10	91	GAVGDGKHDCTEAFST	0
46	NPAPGTLRYGATDRP	20	92	DCTEAFSTAWQAACKN	30
47	YGATDRPLWIIFSGN	30	93	AWQAACKNPSAMLLVP	30
48	LWIIFSGNMNIKLKMP	60	94	PSAMLLVPGSKKFVFN	30
49	MNIKLKMPMYIAGYKT	20	95	GSKKFVNNLFFNGPC	30
50	MYIAGYKTFDGRGAQV	20	96	NLFFNGPCQPHFTFKV	10
51	FDGRGAQVYIGNGGPC	60	97	QPHFTFKVDGIIAAYQ	60
52	YIGNGGPCVFIKRVS	30	98	DGIIAAYQNPASWKNN	70
53	VFIKRVSNNIIGHLYL	50	99	NPASWKNNRIWLQFAK	50
54	VIIIGHLYLGCSTSVL	20	100	RIWLQFAKLTGFTLMG	40
55	YGCSTSVLGNVLINES	0	101	LTGFTLMGKGVIDGQG	10
56	GNVLINESFGVEPVHP	30	102	KGVIDGQGKQWWAGQC	10
57	FGVEPVHPQDGDALT	20	103	KQWWAGQCKWVNGREI	10
58	QDGDALTRTATNIWI	20	104	KWVNGREICNDRDRPT	20
59	RTATNIWIDHNSFSNS	40	105	CNDRDRPTAIKDFST	20
60	DHNSFSNSSDGLVDVT	30	106	AIKDFSTGLIIQGLK	30
61	SDGLVDVTLTSTGVTI	20	107	GLIIQGLKLMNSPEFH	30
62	LTSTGVTISNNLFFNH	10	108	LMNSPEFHLVFGNCEG	30

Cry j 1			Cry j 2		
SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)	SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)
63	SNNLFFNHHKVMLLGH	30	109	LVFGNCEGVKIIGISI	30
64	HKVMLLGHHDDAYSDDK	0	110	VKIIGISITAPRDSNP	50
65	DDAYSDDKSMKVTVAF	20	111	TAPRDSNPNTDGIDIFA	10
66	SMKVTVAFNQFGPNCG	40	112	TDGIDIFASKNFHLQK	20
67	NQFGPNCGQRMPPRY	0	113	SKNFHLQKNTIGTGDD	30
68	QRMPPRYGLVHVANN	20	114	NTIGTGDDCVAIGTGS	10
69	GLVHVANNNDPWTIY	30	115	CVAIGTGSSNIVIEDL	10
70	NYDPWTIYAIGGSSNP	10	116	SNIVIEDLICGPGHGI	30
71	AIGGSSNPILSEGENS	10	117	ICGPGHGISIGSLGRE	0
72	TILSEGENSFTAPNESY	60	118	SIGSLGRENSRAEVS	40
73	FTAPNESYKKQVTIRI	20	119	NSRAEVSYPHVNGAKF	50
74	KKQVTIRIGCKTSSSC	20	120	VHVNGAKFIDTQNGLR	30
75	GCKTSSSCSNVWVQST	0	121	IDTQNGLRITWQGG	0
76	SNVWVQSTQDVFYNGA	60	122	IKTWQGGSGMASHIY	0
77	QDVFYNGAYFVSSGKY	50	123	GMASHIYENVEMINS	10
78	YFVSSGKYEGGNIYTK	30	124	ENVEMINSENPIILNQ	10
79	EGGNIYTKKEAFNVEN	50	125	ENPIILNQFYCTSASA	20
80	KEAFNVENGNA TPQLT	40	126	FYCTSASACQNQRSAV	10
81	GNATPQLTKNAGVLTC	50	127	CQNQRSAVQIQDVITYK	20
82	LTKNAGVLTCSLSKRC	30	128	QIQDVITYKNIRGTSAT	30
			129	NIRGTSATAAAIQLKC	20
			130	AAAIQLKCSDSMPCKD	10
			131	SDSMPCKDIKLSDSL	0
			132	IKLSDSLKLTSGKIA	40
			133	KLTSGKIASCLNDNAN	50
			134	SCLNDNANGYFSGHVI	0
			135	GYFSGHVIPACKNLSP	0
			136	PACKNLSPSAKRKESK	10
			137	SAKRKESKSHKHPKTV	0
			138	SHKHPKTMVENMRAY	0
			139	MVENMRAYDKGNRTRI	0
			140	DKGNRTRILLGSRPPN	10
			141	LLGSRPPNCTNKCHGC	0
			142	CTNKCHGCSPCKAKLV	0
			143	SPCKAKLVIVHRIMPQ	0
			144	IVHRIMPQEYYPQRWI	0
			145	EYYPQRWICSCHGKIY	10

Cry j 1			Cry j 2		
SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)	SEQ ID NO:	Peptide Sequence	T-cell donor coverage (n=10)
			146	YPQRWICSCHGKIYHP	10

Example 2 – design of modified peptides to improve aqueous solubility

This example describes how peptides are re-designed to improve aqueous solubility, in particular to increase the solubility in an aqueous solution having pH in a physiologically acceptable range, e.g. from 4.5 to 8.5. Solubility is closely related to the ratio between hydrophilic and hydrophobic amino acid, the number of charged amino acids and the net charge of the peptide at a given pH. Peptides have zero net charge at pH = pI, and would be expected to show the lowest solubility at this pH.

Peptides are preferably elongated with amino acid residues naturally encoded within the full length allergen sequences i.e. Cry j 1, Cry j 2, Cha o 1 or Cha o 2. The peptides shown in the following examples were elongated using isoform sequences Cry j 1.0101 (SEQ ID NO: 1) and Cry j 2.0101 (SEQ ID NO: 3), as templates.

In cases where peptides are not easily improvable by elongation by the natural allergen-encoding sequence (as there are no charged amino acids in close proximity to the peptide within the allergen sequence) peptide-solubility is improved by addition of either non-encoding negatively charged amino acids or non-encoded positively charged amino acids. Finally, examples where these two combinations are applied (i.e. natural elongation and addition of non-encoded amino acids) are also shown.

Examples of designed variants are shown in the tables below and where:

"Modification" shows the modification to a peptide, if any. Addition of allergen-encoded amino acids are underlined and non-coded amino acids are shown in bold.

"pI" shows the isoelectric point of the peptide or variant

"Charge" shows the overall net charge of the peptide or variant at pH 7

"HR, %" describes the number of hydrophobic amino acid residues in a peptide or variant shown in percentage.

"Pred Sol" shows the predicted solubility of the peptide or variant. 0: Expected/predicted to show relatively poor aqueous solubility, +: Expected/predicted to show good aqueous solubility (several + means increasing predicted solubility)

- 5 Modification of peptide SEQ ID NO: 48: This peptide has a relatively high percentage of hydrophobic amino acids and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2a. Peptide 48 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
48	LWIIIFSGNMNIKLKMP	Parent peptide	6.7	+2	56	0
148	<u>RDRPL</u> WIIIFSGNMNIKLKMP	Allergen-encoded <u>RDRP</u> added	10.6	+3	45	+
149	<u>RRDRPL</u> WIIIFSGNMNIKLKMP R	Allergen-encoded <u>RDRP</u> added Non-encoded R added to N- and C-terminus	11.7	+5	41	+++

- 10 The parent peptide (peptide SEQ ID NO: 48) is improved by addition of several hydrophilic and charged amino acids, encoded by the natural allergen sequence (see peptide SEQ ID NO: 148). Predicted/expected solubility is further improved by addition of two positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 149).

- 15 Modification of peptide SEQ ID NO: 13: This peptide has a relatively high percentage of hydrophobic amino acids and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2b. Peptide 13 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
13	SRAEVSYPHVNGAKF	Parent peptide	9.5	1.1	47	+
203	<u>REN</u> SRAEVSYPHVNGAKF <u>ID</u>	Allergen-encoded <u>REN</u> and <u>ID</u> added	7.5	0.1	40	++
204	<u>RREN</u> SRAEVSYPHVNGAKF <u>IDR</u>	Allergen-encoded <u>REN</u>	10.4	2.1	36	++++

		and <u>ID</u> added. Non-encoded R added to N- and C-terminus				
--	--	--	--	--	--	--

The parent peptide (peptide SEQ ID NO: 13) is improved by addition of several hydrophilic and charged amino acids, encoded by the natural allergen sequence (see peptide SEQ ID NO: 203). Predicted/expected solubility is further improved by addition of two positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 204).

Modification of peptide SEQ ID NO: 25: This peptide has a relatively high percentage of hydrophobic amino acids and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2c. Peptide 25 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
25	NNRIWLQFAKLTGFT	Parent peptide	11.4	2	47	0
189	<u>K</u> NNRIWLQFAKLTGFT	Allergen-encoded <u>K</u> added	11.6	3	44	+
190	R <u>K</u> NNRIWLQFAKLTGFT RR	Allergen-encoded <u>K</u> added. One non-encoded R added to N-terminus and two R added to C-terminus	12.6	6	37	++++

The parent peptide (peptide SEQ ID NO: 25) is improved by addition of one hydrophilic and positively charged amino acid, encoded by the natural allergen sequence (see peptide SEQ ID NO: 189). Predicted/expected solubility is further improved by addition of three positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 190).

Modification of peptide SEQ ID NO: 27: This peptide has a relatively high percentage of hydrophobic amino acids and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2d. Peptide 27 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
27	GIDIFASKNFHLQKN	Parent peptide	9.9	1.1	40	+
200	<u>RDSPNTD</u> GIDIFASKNFHLQKN	Allergen-encoded <u>RDSPNTD</u> added	7.5	0.1	27	+++
201	<u>RRDSPNTD</u> GIDIFASKNFHLQKN R	Allergen-encoded <u>RDSPNTD</u> added. Non-encoded R added to N- and C-terminus	10.6	2.1	25 %	++++ +

The parent peptide (peptide SEQ ID NO: 27) is improved by addition of several hydrophilic and charged amino acids, encoded by the natural allergen sequence (see peptide SEQ ID NO: 200).

- 5 Predicted/expected solubility is further improved by addition of two positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 201).

Modification of peptide SEQ ID NO: 17: This peptide has a high percentage of hydrophobic amino acids and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2e. Peptide 17 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
17	IFSKNLNIKLNMPLYIAGNK	Parent peptide	10.6	3	50	0
150	RRIFS KNLNIKLNMPLYIAGN KR	Two non-encoded R added to N-terminus and one R added to C-terminus	11.9	6	44	+++

10

As there are no charged amino acids in close proximity to the parent peptide (peptide SEQ ID 17) within the allergen sequence, improvement is made by addition of three positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 150).

Modification of peptide SEQ ID NO: 97: This peptide has a high percentage of hydrophobic amino acids, has almost zero charge at pH 7 and contains only a few charged amino acids, so is likely to benefit from an optimization:

Table 2f. Peptide 97 and variants

Peptide SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
97	QPHFTFKVDGIIAAYQ	Parent peptide	7.5	0.1	50 %	0
184	RRQPHFTFKVDGIIAAYQR	Two non-encoded R added to N-terminus and one R added to C-terminus	11.2	3.1	42 %	+++

5

As there are no charged amino acids in close proximity to the parent peptide (peptide SEQ ID NO: 97) within the allergen sequence, improvement is made by addition of three positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 184).

Modification of peptide SEQ ID NO: 107: This peptide has a high percentage of hydrophobic amino acids, has almost zero charge at pH 7 and contains only a few charged amino acids, so is likely to benefit from an optimization:

10

Table 2g. Peptide 107 and variants

SEQ ID NO:	Amino acid sequence	Modification	pI	Charge	HR %	Pred sol
107	GLIIQGLKLMNSPEFH	Parent peptide	7.8	0.1	44 %	0
195	RRGLIIQGLKLMNSPEFHR	Two non-encoded R added to N-terminus and one R added to C-terminus	11.8	3.1	37 %	+++
196	<u>KDFDST</u> GLIIQGLKLMNSPEFH	Allergen-encoded <u>KDFDST</u> added	7.6	0.1	41 %	+
197	RR <u>KDFDST</u> GLIIQGLKLMNSPEFHR	Allergen-encoded <u>KDFDST</u> added Two non-encoded R added to N-terminus and one R added to C-terminus	11.3	3.1	36 %	++++

The parent peptide (peptide SEQ ID NO: 107) is improved by addition of several hydrophilic and charged amino acids, encoded by the natural allergen sequence (see peptide SEQ ID NO: 196). However this additional stretch of amino acids (KFDFST) also contain two highly hydrophobic amino acids (two F) which may contribute negatively to the overall aqueous solubility. Therefore, predicted/expected solubility is further improved by addition of three positively charged non-encoded Argenines (R) (see peptide SEQ ID NO: 197). Finally, a peptide variant of the parent peptide (peptide SEQ ID NO: 107) that is elongated by three non-encoded positively charged Argenines (R) is also shown (see peptide SEQ ID NO: 195).

Example 3 Solubility assessment of peptides

To evaluate aqueous solubility of a selection of peptides, peptides were provided (by GenScript, USA) as acetate salts, >95 % purity at a 20mg scale. Test samples with a peptide concentration of 3 mg/mL (dry matter) were produced with the following solvents: Buffer 1; Water, Buffer 2; Acetate buffer, pH 4.5 (25 mM sodium acetate containing 250 mM D-Mannitol), pH 4.5, Buffer 3; 25 mM histidine buffer, pH 7.0, Buffer 4; Glycine buffer, pH 8.5 (35 mM glycine containing 250 mM D-Mannitol)

The solubility of the peptides was initially investigated by visual inspection of the test samples. Visual inspection included assessment of turbidity and presence of particles/aggregates of the test sample before versus after filtration of the test samples. Filtration of test samples were conducted using syringe based filters containing a polyethersulfone (PES) membrane with a pore size of 0.2µm. The visual inspection was scored as "large precipitate": score 0, "small/few precipitates": score 1 and "clear solution": score 2. If large precipitates were observed – no further analysis was performed. Peptide samples with a score of 1 and 2 in visual evaluation were further evaluated by U-HPLC (described further below) and Photobox analysis which is a more in-depth visual characterization method where the sample is illuminated by a LED light source from the bottom of the sample-vial and light scattering is measured via a digital camera (everything encapsulated inside a light-tight, dark box). The Photobox was used to further support the visual inspection with quantitative data from the pixel analysis compared to a reference (Stabcal® Turbidity Standard, 20.0 NTU, Hach, USA). Samples with pixels number below the reference was scored 1 and pixel numbers> reference was score 0.

The amount of dissolved peptide was measured by U-HPLC analysis by reverse phase chromatography (Ultimate 3000/C18 column, Thermo Fischer Scientific, USA). The recovery of the test samples were calculated as the area of the main peak compared to the area of the main peak

of a reference (peptide dissolved in an organic solvent assuming 100% solubility). Similar the filter recovery was addressed by measuring the main peak area of the test sample before and after filtration. The following scores were applied based on the un-filtered HPLC recovery to a reference:

- 5 +/-20%: 2, 20-50%: 1, >50%: 0. For the filter recovery the following scores were applied: +/-15%: 2, 15-50%: 1, >50% : 0. Results from all analysis are summarized in table 3. Each peptides is assigned a total score (visual, photobox and U-HPLC) between 0-7 for each buffer as follows: 0-2 Poor solubility, 3-5 medium solubility, may be able to add excipients to increase solubility and 6-7 Good solubility.

- 10 The best obtained score in buffers 2, 3 or 4 is shown ("Best Score") and peptide or variant is denoted soluble or not if it is soluble in at least one of the buffer 2-4 ("Soluble") and not soluble if only soluble in buffer exclusively.

Table 3. Results of solubility test of a selection of peptides

Allergen	SEQ ID NO:	Sequence	Add. ID	pI	Best Score	Soluble
Cry j 2	11	IIQGLKLMNSPEFHL	B001	7.8	7	YES
Cry j 2	107	GLIIQGLKLMNSPEFH	B002	7.8	0	NO
Cry j 2	194	RRIIQGLKLMNSPEFHLR	B003	11.8	7	YES
Cry j 2	195	RRGLIIQGLKLMNSPEFHR	B004	11.8	7	YES
Cry j 2	196	KFDFSTGLIIQGLKLMNSPEFH	B005	7.6	2	NO
Cry j 2	197	RRKFDFSTGLIIQGLKLMNSPEFHR	B006	11.3	NA	NA
Cry j 2	97	QPHFTFKVDGIIAAYQ	B007	7.5	NA	NA
Cry j 2	184	RRQPHFTFKVDGIIAAYQR	B008	11.2	7	YES
Cry j 2	214	ENPILINQFYSTSASA	B009	0.9	NA	NA
Cry j 2	207	DENPILINQFYSTSASADD	B010	0.6	6	YES
Cry j 2	208	RRENPIINQFYSTSASAR	B011	10.9	3	NO
Cry j 1	48	LWIIIFSGNMNIKMKMP	B012	10.7	NA	NA
Cry j 1	148	RDRPLWIIIFSGNMNIKMKMP	B013	11.4	7	YES
Cry j 1	149	RRDRPLWIIIFSGNMNIKMKMPR	B014	12.1	4	NO
Cry j 1	56	GNVLINESFGVEPVHP	B015	4.1	7	YES
Cry j 1	154	GNVLINESFGVEPVHPQDGD	B016	3.4	7	YES
Cry j 1	155	GNVLINESFGVEPVHPQD	B017	3.7	7	YES
Cry j 1	156	DEGNVLINESFGVEPVHPQDD	B018	3.2	7	YES
Cry j 1	157	RRGNVLINESFGVEPVHPR	B019	10.3	7	YES
Cry j 1	5	DALTLRTATNIWIDHNSFSN	B020	5.0	NA	NA
Cry j 1	158	DDALTLRTATNIWIDHNSFSNDD	B021	3.5	7	YES
Cry j 1	159	RRDALTLRTATNIWIDHNSFSNR	B022	11.6	3	NO
Cry j 1	59	RTATNIWIDHNSFSNS	B023	7.5	0	NO
Cry j 1	160	RTATNIWIDHNSFSNSSDGLVD	B024	4.0	0	NO
Cry j 1	161	DRTATNIWIDHNSFSNSSDGLVDD	B025	3.5	6	YES
Cry j 1	9	DVFYNGAYFVSSGKYEGGNI	B026	3.9	4	NO
Cry j 1	178	DVFYNGAYFVSSGKYEGGNIYTKKE	B027	6.9	0	NO

Allergen	SEQ ID NO:	Sequence	Add. ID	pI	Best Score	Soluble
Cry j 1	77	QDVFYNGAYFVSSGKY	B028	6.3	NA	NA
Cry j 1	176	DDQDVFYNGAYFVSSGKYED	B029	3.2	7	YES
Cry j 1	177	RRQDVFYNGAYFVSSGKYER	B030	9.8	4	NO
Cha o 1	18	HFFNHHKVMMLGHSDIYSDD	B031	6.1	0	NO
Cha o 1	163	HFFNHHKVMMLGHSDIYSDDK	B032	6.5	0	NO
Cha o 1	164	DDHFFNHHKVMMLGHSDIYSDDK	B033	5.6	7	YES
Cha o 1	165	RHFFNHHKVMMLGHSDIYSDDKR	B034	9.4	7	YES
Cry j 2	26	AIKDFSTGLIIQGL	B035	6.7	NA	NA
Cry j 2	191	RDRPTAIKDFSTGLIIQGLK	B036	10.6	NA	NA
Cry j 2	192	RRDRPTAIKDFSTGLIIQGLKR	B037	11.7	7	YES
Cry j 2	27	GIDIFASKNFHLQKN	B038	9.9	0	NO
Cry j 2	200	RDSPNTDGIDIFASKNFHLQKN	B039	7.5	7	YES
Cry j 2	201	RRDSPNTDGIDIFASKNFHLQKNR	B040	10.6	7	YES
Cry j 2	13	SRAEVSYPVHNGAKF	B041	9.5	5	NO
Cry j 2	203	RENSRAEVSYPVHNGAKFID	B042	7.5	6	YES
Cry j 2	204	RRENSRAEVSYPVHNGAKFIDR	B043	10.4	7	YES
Cry j 2	25	NNRIWLQFAKLTGFT	B044	11.4	6	YES
Cry j 2	189	KNNRIWLQFAKLTGFT	B045	11.6	7	YES
Cry j 2	190	RKNNRIWLQFAKLTGFTRR	B046	12.6	7	YES
Cry j 2	12	ASKNFHLQKNTIGTG	B047	10.7	7	YES
Cry j 2	205	ASKNFHLQKNTIGTGDD	B048	7.8	7	YES
Cry j 2	206	RASKNFHLQKNTIGTGDDR	B049	10.6	7	YES
Cry j 2	14	SKDIKLSDSLKLTS	B050	9.6	6	YES
Cry j 2	212	SKDIKLSDSLKLTSKG	B051	10.2	6	YES
Cha o 1	17	IFSKNLNIKLNMPLYIAGNK	B052	10.6	6	YES
Cha o 1	150	RRIFSKNLNIKLNMPLYIAGNKR	B053	11.9	7	YES
Cry j 1	6	KSMKVTVAFNQFGPNSGQRM	B054	11.6	7	YES
Cry j 1	167	DDKSMKVTVAFNQFGPNSGQRMPR	B055	10.7	6	YES
Cry j 1	66	SMKVTVAFNQFGPNSG	B056	9.9	0	NO
Cry j 1	168	KSMKVTVAFNQFGPNSGQR	B057	11.6	7	YES
Cry j 1	170	DDKSMKVTVAFNQFGPNSGQR	B058	10.0	NA	NA
Cry j 1	171	GQRMPRARYGLVHVANN	B059	11.8	7	YES
Cry j 1	172	RQRMPRARYGLVHVANNR	B060	12.3	NA	NA
Cry j 2	173	VDGIIAAYQNPASWK	B061	6.6	7	YES
Cry j 2	10	KVDGIIAAYQNPASWKNNR	B062	10.2	7	YES
Cry j 2	185	RKVDGIIAAYQNPASWKNNRR	B063	11.3	7	YES
Cry j 2	186	RRVDGIIAAYQNPASWKRR	B064	11.2	NA	NA

The results show that it was possible to design peptide variants that by experimental evaluation showed enhanced aqueous solubility. In most cases one or more peptide variants of each parent peptide were even scored 7 (max score) under all tested conditions, hence, demonstrating good aqueous solubility in a very broad pH-range (4.5-8.5). However, good aqueous solubility of the best peptide variant of a few parent peptides was limited to a more narrow pH range e.g. variant (SEQ

ID NO: 158) of parent peptide SEQ ID NO: 5 that showed good solubility at pH 8.5; variant (SEQ ID NO: 176) of parent peptide SEQ ID NO: 77 that showed good solubility at pH 6.5-8.5; variant (SEQ ID NO: 164) of parent peptide SEQ ID NO: 18 that showed good solubility at pH 4.5 and 8.5 (but not at pH 6.5) (data not shown). Thus, peptide mixes containing these latter variant peptides are expected to have a more restricted formulation-design space in terms of a more limited pH range compared to the peptide variants that showed good aqueous solubility in a broader pH range. Notably, peptides with SEQ ID NOs: 157, 185, 190 and 194 has very good solubility and thus preferable.

Example 4 In vitro HLA Class II binding analysis of peptides

This example describes how to determine the HLA class II binding of peptides of the invention.

The assay employed is a competitive MHC class II binding assay, wherein each peptide is analyzed for its ability to displace a known control binder from each of the human MHC class II allotypes shown in example 5, Table 4. Due to the nature of the competitive assay, the data for each peptide is determined as a ratio of its own IC_{50} to that of the control peptide. Thus, a peptide that has an IC_{50} value that is parity to the control peptide has an identical binding affinity, while peptides with a ratio less than one have a higher affinity and those with a ratio greater than one have a lower affinity. The ratio of IC_{50} may be determined at different cutoff concentrations such as 300-1000 nM. In this example a cutoff of 300 nM was employed.

Assays to quantitatively measure peptide binding to purified class II MHC molecules are based on the inhibition of binding of a high affinity radiolabeled peptide to purified MHC molecules, and were performed essentially as detailed elsewhere (Sidney et al. 2008; Sidney et al. 2010a, Sidney et al. 2010b; Greenbaum et al. 2011; Sidney et al. 2001. Sidney et al 2013. McKinney et al 2013). Briefly, 0.1–1 nM of radiolabeled peptide was co-incubated at room temperature or 37°C with purified MHC in the presence of a cocktail of protease inhibitors. Following a two- to four-day incubation, MHC bound radioactivity was determined by capturing MHC/peptide complexes on monoclonal Ab coated Lumitrac 600 plates (Greiner Bio-one, Frickenhausen, Germany) and measuring bound cpm using the TopCount (Packard Instrument Co., Meriden, CT) microscintillation counter. In the case of competitive assays, the concentration of peptide yielding 50% inhibition of the binding of the radiolabeled peptide was calculated. Under the conditions utilized, where $[label] < [MHC]$ and $IC_{50} \geq [MHC]$, the measured IC_{50} values are reasonable approximations of the true K_d values. Each peptide was tested at six different concentrations covering a 100,000-fold dose range in three or more independent experiments. As a positive control, the unlabeled version of the radiolabeled probe was also tested in each experiment.

The 26 HLA Class II alleles used for binding assay were HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101, DRB5_0101. In the Table 4 below, only the beta-chain is referred to when identified which allele the peptides bind to.

The IC₅₀ value of each peptide towards each of 28 alleles was determined by the above described method and is shown in Table 4 below. Peptides with an IC₅₀ value below 300 nM measured against a given HLA were considered as binding towards this HLA, and this is indicated by "x" in the table.

Table 4. HLA binding data

In vitro HLA Class II binding of a selection of peptides																											
SEQ ID NO:	DPB1 02:01	DPB1 03:01	DPB1 04:01	DPB1 04:02	DPB1 05:01	DPB1 14:01	DQB1 02:01	DQB1 03:01	DQB1 03:02	DQB1 05:01	DQB1 06:02	DRB1 01:01	DRB1 03:01	DRB1 04:01	DRB1 04:05	DRB1 07:01	DRB1 08:02	DRB1 09:01	DRB1 11:01	DRB1 12:01	DRB1 13:02	DRB1 15:01	DRB3 01:01	DRB3 02:02	DRB4 01:01	DRB5 01:01	
5		x									x	x			x	x		x			x	x			x		
7		x						x				x		x	x	x	x	x	x	x		x			x	x	
25			x	x	x							x	x				x	x	x			x			x	x	
27	x		x	x								x		x	x	x	x	x	x			x			x	x	
48	x		x	x	x							x			x	x		x	x		x	x		x		x	
49	x		x		x	x						x					x	x	x	x		x		x	x	x	
51								x			x	x										x		x			
53	x	x	x	x		x					x	x			x	x		x			x	x		x	x	x	
56	x		x	x						x		x		x		x		x			x	x		x	x		
63				x	x						x	x				x	x	x	x		x	x			x		
66	x		x		x											x											
72											x	x		x	x			x				x					
76										x		x			x			x							x		
77	x		x		x			x				x					x	x	x		x	x		x		x	
81								x				x									x			x			
82												x				x	x	x	x		x	x				x	
92																		x								x	
95	x		x		x														x					x			
97			x	x		x						x	x	x	x	x	x	x	x				x	x	x	x	
98	x		x	x		x		x		x	x	x		x	x		x	x				x		x	x	x	
100	x		x	x	x					x	x	x			x	x	x	x	x	x		x			x	x	
106	x		x	x		x					x	x				x		x	x		x	x	x		x		
107				x							x	x			x		x	x	x	x		x			x		
113												x		x	x		x		x			x		x	x	x	

In vitro HLA Class II binding of a selection of peptides																											
SEQ ID NO.		DPB1 02:01	DPB1 03:01	DPB1 04:01	DPB1 04:02	DPB1 05:01	DPB1 14:01	DQB1 02:01	DQB1 03:01	DQB1 03:02	DQB1 05:01	DQB1 06:02	DRB1 01:01	DRB1 03:01	DRB1 04:01	DRB1 04:05	DRB1 07:01	DRB1 08:02	DRB1 09:01	DRB1 11:01	DRB1 12:01	DRB1 13:02	DRB1 15:01	DRB3 01:01	DRB3 02:02	DRB4 01:01	DRB5 01:01
119			x	x					x			x	x		x	x	x	x	x	x		x	x	x	x	x	x
125	x												x		x	x	x		x			x	x		x	x	
129			x				x		x			x	x				x		x				x			x	
133																							x	x			

Example 5 Estimated HLA coverage of individual peptides

This example describes how HLA Class II allele coverage are determined for individual peptides disclosed herein.

- 5 In order to elicit a T cell response a given peptide must be able to bind to at least one HLA class II molecule in a given individual. Each individual express several HLA molecules, and globally (worldwide), thousands of different alleles exist. Each HLA molecule can bind a limited number of different peptides and not all HLAs bind the same peptides. In order to estimate the potential coverage of a peptide in a given population, the frequency of the different HLA class II molecules
10 present in the population, and the binding affinity of the peptide towards each of these molecules must be available.

The present estimation is either based on the alleles of a worldwide population or Japanese population shown in Table 4 below. The peptide binding to a specific HLA molecule can be experimentally measured, for example as described in Example 4, or predicted using *in silico*
15 algorithms as e.g. NetMHCIIpan-3.1 (Massimo Andreatta et al. 2015).

The exact affinity necessary for an immune response is not known, but it is generally assumed to be below 1000nM. For predicting the affinities of the peptides disclosed herein we used the NetMHCIIpan-3.1 algorithm. To assign a given peptide as a binder for a given HLA we used a binding threshold of 300 nM together with the percentile rank score reported in this algorithm of at
20 least 30.

Assuming that alleles at different loci are independently distributed in the worldwide population (which is not entirely true, but is a reasonable approximation), the phenotypic coverage of the binding alleles were calculated using standard methods known in the art. For example, for each HLA locus (DRB1, DRB3, DRB4, DRB5) or locus combination (DQA1-DQB1, DPA1-DPB1), the HLA
25 allele frequencies of all the alleles from the given locus found to bind the given peptide is summed ($f_{\text{sum,locus}}$). The total phenotypic coverage for each locus, n (C_n) is calculated as $(2 \times f_{\text{sum,locus}}) - (f_{\text{sum,locus}})^2$.

The total phenotypic coverage of all binding alleles from n loci can be calculated as

$$K_n = \sum_{i=1}^n K_{(i-1)+} (1 - K_{(i-1)}) \times C_i, \text{ where } K_0 = 0$$

The following parameters were calculated to express the HLA class II binding properties of each of the peptides:

A: Binding coverage of world wide population (Bind Cov WW, 300 nM)

This parameter express the fraction or percentage of the world-wide population which may express one or more the HLA molecules experimentally measured to bind a peptide, for example as described in Example 8.

For example, peptide with SEQ ID NO: 5 have been experimentally determined to bind to the following 9 HLA molecules: DPB1_0301, DQB1_0602, DRB1_0101, DRB1_0405, DRB1_0701, DRB1_0901, DRB1_1302, DRB1_1501, and DRB4_0101 with an affinity stronger than 300 nM (table 4 of example 4). Using the allele frequencies for a world wide population displayed in Table 5 below the allele frequency sum for each locus is; DRB1: 0,3255, DRB3: 0,0, DRB4: 0,237, DRB5: 0,0, DP: 0,07, and DQ: 0,076. Each Locus Coverage can then be calculated, e.g., DRB1: $(2 \times 0,3255) - (0,3255 \times 0,3255) = 0.545$. Likewise the remaining locus coverages can be calculated as DRB3: 0, DRB4: 0,418, DRB5: 0, DP: 0,135, and DQ: 0,146. Given the above formula this will can be calculated setting DRB1=C₁, DRB3=C₂, DRB4=C₃, DRB5=C₄, DP=C₅, DQ=C₆:

$$K_0 = 0,$$

$$K_1 = K_0 + (1 - K_0) * C_1 = 0,545 + (1-0)*0,545 = 0.545$$

$$K_2 = K_1 + (1 - K_1) * C_2 = 0,545 + (1-0,545)*0 = 0.545$$

$$K_3 = K_2 + (1 - K_2) * C_3 = 0,545 + (1-0,545)*0,418 = 0.735$$

$$K_4 = K_3 + (1 - K_3) * C_4 = 0,735 + (1-0,735)*0 = 0.735$$

$$K_5 = K_4 + (1 - K_4) * C_5 = 0,735 + (1-0,735)*0,135 = 0.771$$

$$K_6 = K_5 + (1 - K_5) * C_6 = 0,771 + (1-0,771)*0,146 = 0.804,$$

meaning that at least 80.4% of the world-wide population will express one or more the 9 HLA alleles that bind peptide # 5 with an affinity stronger than 300 nM.

B: Binding coverage of Japanese population (Bind Cov Jap, 300 nM)

This parameter express the fraction or percentage of the Japanese population which may express one or more the HLA molecules experimentally measured to bind a peptide, for example as described in Example 4.

For example, the peptide with SEQ ID NO: 5 have been experimentally determined to bind to to following 9 HLA molecules: DPB1_0301, DQB1_0602, DRB1_0101, DRB1_0405, DRB1_0701, DRB1_0901, DRB1_1302, DRB1_1501, and DRB4_0101 with an affinity stronger than 300 nM (table XXX). Using the allele frequencies for a Japanese population displayed in Table 5 the allele

frequency sum for each locus is; DRB1: 0.4766, DRB3: 0.0, DRB4: 0. DRB5: 0.0, DP: 0.01324, and DQ: 0.01033. DRB4_0101 have not been found in the population studies behind the frequencies (NULL) and are thus given a frequency of 0. Each Locus Coverage is then DRB1: 0.726, DRB3: 0, DRB4: 0, DRB5: 0, DP: 0.0263, and DQ: 0.0255. Given the above formula this will be calculated to 0.739 = 73.9% coverage, meaning that at least 73.9 % of the Japanese population will express one or more the 9 HLA alleles that bind peptide # 5 with an affinity stronger than 300 nM

C: Predicted coverage of worldwide population (Pred Cov WW)

This parameter express the fraction or percentage of the worldwide population which may express one or more the HLA molecules in silico predicted to bind a peptide. This is determined using the alleles and allele frequencies of a worldwide population (240 alleles and allele frequencies shown in Table 5)

Predicted affinity is obtained using the in silico tool NetMHCIIpan-3.1. All peptides are predicted as sub-15mers as is default for the tool. For longer peptides, like peptide # 5, the peptide are predicted to have the binding affinity and rank of the best binding sub-15mer. Peptide # 5 with the sequence DALTLRTATNIWIDHNSFSN, will then be predicted as DALTLRTATNIWIDH, ALTLRTATNIWIDHN, LTLRTATNIWIDHNS, TLRTATNIWIDHNSF, LRTATNIWIDHNSFS, and RTATNIWIDHNSFSN, respectively. For the allele DRB1_0101 the best predicted sub-15mer is DALTLRTATNIWIDH. which have a predicted affinity of 56,86 nM and a predicted rank percentile of 19. As both measures are below the cutoff of 300 nM and 30%, respectively, peptide # 5 is predicted to bind to DRB1_0101. Similar predictions are performed regarding each of the HLA molecules in table 5 for which the WW HLA frequency is available (i.e. not NULL in table 5), and indicated with a cross in in table 5. Peptide #5 is predicted to bind 34 of the 63 HLA-DRB1 molecules, and the HLA-DQA10102-DQB10602 molecule, but none of the two DRB3 molecules, the DRB4_0101 molecule, the DRB5_0101 molecule nor any of the 7 HLA-DP molecules. This gives a predicted locus frequency sum for DRB1 of 0.6222 and thereby a DRB1 locus coverage of 0.857. HLA-DQ frequency is 0.076 giving a locus coverage of 0.146 and the residual locus sums are 0. This leads to an overall predicted world wide HLA coverage of 87.8%.

D: Predicted coverage of Japanese population (Pred Cov Jap)

This parameter express the fraction or percentage of the Japanese population which may express one or more the HLA molecules in silico predicted to bind a peptide. This is determined using the alleles and allele frequencies of a Japanese population shown in Table 5). Predicted affinity is obtained as described above for predicted coverage of worldwide population for which the Japanese HLA frequency is available (i.e. not NULL in Table 5), and indicated with a cross (x) in Table 5. Peptide #5 is predicted to bind 20 of the 42 HLA-DRB1 molecules, 16 of the 119 HLA-DQ molecules, and none of the 45 HLA-DP molecules. No DRB3, 4 or 5 allele frequencies are used for

the Japanese population due to lack of availability. This gives a predicted locus frequency sum for DRB1 of 0.6556 and thereby a DRB1 locus coverage of 0.881. HLA-DQ locus frequency sum is 0.03668 giving a locus coverage of 0.072. The rest of the loci frequency sums are 0. This leads to an overall predicted world wide HLA coverage of 89.0%.

5 E: Predicted coverage of worldwide population (Pred Cov WW, 28 HLA's)

This parameter express the fraction or percentage of the worldwide population which may express one or more the HLA molecules in silico predicted to bind a peptide, wherein this is determined using a subset of 28 of the most frequent alleles of a worldwide population shown in Table 5, indicated by an asterisk. This subset is the same used for determining in vitro binding.

- 10 Predicting HLA coverage using this subset gives an indication of the HLA coverage obtained by binding experiments. The 28 alleles are a true subset of the alleles used for the predicted HLA coverage. Of the 11 DRB1 alleles in the binding panel, 8 are predicted to bind to peptide # 5: DRB1_0101, DRB1_0401, DRB1_0701, DRB1_0901, DRB1_1201, DRB1_1302, DRB1_1501, and DRB1_0405. This results in a locus frequency sum of 0,3825 and a DRB1 locus coverage of 0,6187.
- 15 No DRB3, -4 or -5 molecules, or any HLA-DP molecules are predicted to bind. The only HLA-DQ molecule with a WW frequency predicted to bind, HLA-DQA10102-DQB10602, is also part of the binding panel thus the HLA-DQ locus frequency sum is 0.076 and the locus coverage 0.146. The world wide coverage of peptide #5 regarding HLA molecules in the binding panel can thus be calculated to 67.4%.

20 F: Predicted coverage of Japanese population (Pred Cov Jap, 28 HLA's)

The 9 HLA molecules in the binding panel predicted to bind peptide # 5 in the "Pred Cover(WW, 28 bind)" example above are all present in a Japanese population, however with different frequencies of the worldwide as indicated in table 5. Thus for a Japanese population the HLA-DRB1 molecule DRB1_0101, DRB1_0401, DRB1_0701, DRB1_0901, DRB1_1201, DRB1_1302, DRB1_1501, and

25 DRB1_0405 will lead to a locus frequency sum of 0.5238 and a DRB1 locus coverage of 0.7732. The HLA-DQ locus frequency sum is 0.01033 and the locus coverage 0.0206. The predicted Japanese coverage of peptide #5 regarding HLA molecules in the binding panel can thus be calculated to 77.8%.

- 30 The measures A to F were determined for all peptides described in the T cell screening example 1, the modified peptides for improving solubility of Example 2 as well as a number of peptides known to provide a T cell response in a cedar allergic donor from the following publications:

- Sone et al., *J Immunol.* 1998; 161:448-457
- Sone et al., *Allerg. Int.* 2009; 58:237-245

- US patent US2005/0152927
- US patent US2006/0188446

A first pool of peptides disclosed in the above mentioned publications were chosen on the basis of MHC Class II binding predictions, where peptides predicted to bind to alleles covering a high

5 fraction of a worldwide population and showing T cell responses in a high fraction of tested donors.

A secondary pool of peptides were selected among peptides having at least 20% T cell donor coverage or having a predicted HLA-DRB1 coverage >60%. In addition the secondary pool of peptides were selected according to either criteria A and B below.

Criteria A. In this case, a predicted "ALL_Coverage" for HLA binding was calculated, this was multiplied by the fraction of actual responders in the literature, and peptides were selected for which the product of All_Coverage and the responder fraction was greater than 0.4 and in which the DRB1 coverage was at the same time at least 33%.

- ALL_Coverage = Calculated population coverage using predicted peptide binding to alleles from the HLA-DRB1,3,4,5, HLA-DP and HLA-DQ loci.
- Product = fraction responders x ALL_Coverage
- Product > 0.4 AND DRB1 coverage >=33%

Criteria B. In this case, peptides were selected that had a responder fraction greater than 30%, and a predicted DRB1 coverage of more than 33% or an All_coverage of greater than 80%.

The peptides selected by the method described above for the primary and secondary pools are listed below, along with the protein from which they originate.

Primary pool

SEQ ID NO: 5	Cry j 1	DALTLRTATNIWIDHNSFSN
SEQ ID NO: 6	Cry j 1	KSMKVTVAFNQFGPNCQRM
SEQ ID NO: 7	Cry j 1	PRARYGLVHVANNYDPWTI
SEQ ID NO: 8	Cry j 1	CSNWVWQSTQDVFYNGAYFV
SEQ ID NO: 9	Cry j 1	DVFYNGAYFVSSGKYEGGNI
SEQ ID NO: 10	Cry j 2	VDGIIAAYQNPASWK
SEQ ID NO: 11	Cry j 2	IIQGLKLMNSPEFHL
SEQ ID NO: 12	Cry j 2	ASKNFHLQKNTIGTG
SEQ ID NO: 13	Cry j 2	SRAEVSYPVHNGAKF
SEQ ID NO: 14	Cry j 2	CKDIKLSDISLKLTS

Secondary pool

	SEQ ID NO: 15	Cry j 1	YAIGGSSNPTILSEGENSFTA
	SEQ ID NO: 16	Cha o 1	GATRERSLWIIFSKNLNIKL
	SEQ ID NO: 17	Cha o 1	IFSKNLNIKLNMPLYIAGNK
	SEQ ID NO: 18	Cha o 1	HFFNHHKVMMLGHSDIYSDD
5	SEQ ID NO: 19	Cha o 1	KSMKVTVAFNQFGPNAGQRM
	SEQ ID NO: 20	Cha o 1	PRARYGLIHVANNNYDPWSI
	SEQ ID NO: 21	Cha o 1	YAIGGSSNPTILSEGENSFTA
	SEQ ID NO: 22	Cha o 1	SSGKNEGTNIYNNNEAFKVE
	SEQ ID NO: 23	Cha o 1	YNNNEAFKVENGSAAPQLTK
10	SEQ ID NO: 24	Cry j 2	PASWKNNRIWLQFAK
	SEQ ID NO: 25	Cry j 2	NNRIWLQFAKLTGFT
	SEQ ID NO: 26	Cry j 2	AIKFDFSTGLIIQGL
	SEQ ID NO: 27	Cry j 2	GIDIFASKNFHLQKN
	SEQ ID NO: 28	Cry j 2	SYVHVNGAKFIDTQN
15	SEQ ID NO: 29	Cry j 2	LSDISLKLTSKGKIAS
	SEQ ID NO: 30	Cry j 2	GKIASCLNDNANGYF
	SEQ ID NO: 31	Cha o 2	AVLLVPANKKFFVNNLVFRG
	SEQ ID NO: 32	Cha o 2	ARWKNSKIWLQFAQLTDFNL
	SEQ ID NO: 33	Cha o 2	QFAQLTDFNLMGTGVIDGQG
20	SEQ ID NO: 34	Cha o 2	SKSVTVKELTLMNSPEFHLV
	SEQ ID NO: 35	Cha o 2	TGIQLSNVSLKLTSGKPASC
	SEQ ID NO: 36	Cha o 2	VDKNARGFYSGRLIPTCKNL

Table 5. Shows alleles and allele frequencies of a worldwide and Japanese population

* used in in vitro binding assay, + Alleles bind by peptide with SEQ ID NO: 5.

Allele	WW freq	Jap freq	*	+	Allele	WW freq	Jap freq	*	+
DRB1_0101	0.04275	0.0582	*	+	HLA-DQA10101-DQB10201	NULL	0.00189		
DRB1_0102	0.02325	0.0002		+	HLA-DQA10101-DQB10301	NULL	0.01439		
DRB1_0103	0.00475	NULL		+	HLA-DQA10101-DQB10302	NULL	0.01042		
DRB1_0301	0.07725	0.0015	*		HLA-DQA10101-DQB10303	NULL	0.01812		
DRB1_0302	0.0175	NULL			HLA-DQA10101-DQB10401	NULL	0.01804		
DRB1_0307	0.00025	NULL			HLA-DQA10101-DQB10402	NULL	0.00501		
DRB1_0401	0.03375	0.0095	*		HLA-DQA10101-DQB10501	0.076	0.00779	*	
DRB1_0402	0.00775	0.0001			HLA-DQA10101-DQB10502	NULL	0.00263		

Allele	WW freq	Jap freq	*	+	Allele	WW freq	Jap freq	*	+
DRB1_0403	0.01575	0.0306			HLA-DQA10101-DQB10503	NULL	0.00507		
DRB1_0404	0.0275	0.0026			HLA-DQA10101-DQB10601	NULL	0.02097		
DRB1_0405	0.02325	0.1349	*		HLA-DQA10101-DQB10602	NULL	0.0105		
DRB1_0406	0.00625	0.0339			HLA-DQA10101-DQB10603	NULL	0.00097		+
DRB1_0407	0.0245	0.0057			HLA-DQA10101-DQB10604	NULL	0.00683		
DRB1_0408	0.0025	NULL			HLA-DQA10101-DQB10609	NULL	0.00033		
DRB1_0410	0.0025	0.0215		+	HLA-DQA10101-DQB10610	NULL	0.00004		+
DRB1_0411	0.0035	0.0001		+	HLA-DQA10102-DQB10201	NULL	0.00186		
DRB1_0417	0.00025	NULL			HLA-DQA10102-DQB10301	NULL	0.01416		
DRB1_0457	NULL	0.0001		+	HLA-DQA10102-DQB10302	NULL	0.01025		
DRB1_0701	0.1015	0.0034	*	+	HLA-DQA10102-DQB10303	NULL	0.01782		
DRB1_0801	0.01125	NULL		+	HLA-DQA10102-DQB10401	NULL	0.01775		
DRB1_0802	0.02725	0.0421	*		HLA-DQA10102-DQB10402	NULL	0.00492		
DRB1_0803	0.014	0.0832		+	HLA-DQA10102-DQB10501	NULL	0.00766		
DRB1_0804	0.01625	NULL		+	HLA-DQA10102-DQB10502	NULL	0.00259		+
DRB1_0806	0.0015	NULL		+	HLA-DQA10102-DQB10503	NULL	0.00499		
DRB1_0809	0.0005	0.0004			HLA-DQA10102-DQB10601	NULL	0.02063		
DRB1_0811	0.0005	NULL			HLA-DQA10102-DQB10602	0.076	0.01033	*	+
DRB1_0823	NULL	0.0001		+	HLA-DQA10102-DQB10603	NULL	0.00096		+
DRB1_0901	0.0395	0.1428	*	+	HLA-DQA10102-DQB10604	NULL	0.00672		
DRB1_1001	0.017	0.0047		+	HLA-DQA10102-DQB10609	NULL	0.00033		
DRB1_1101	0.057	0.0252	*		HLA-DQA10102-DQB10610	NULL	0.00004		+
DRB1_1102	0.01325	NULL		+	HLA-DQA10103-DQB10201	NULL	0.0026		
DRB1_1103	0.00275	NULL		+	HLA-DQA10103-DQB10301	NULL	0.01977		
DRB1_1104	0.0185	NULL		+	HLA-DQA10103-DQB10302	NULL	0.01431		
DRB1_1106	0.00075	0.0002			HLA-DQA10103-DQB10303	NULL	0.02489		
DRB1_1108	NULL	0.0001			HLA-DQA10103-DQB10401	NULL	0.02479		
DRB1_1110	0.00075	NULL			HLA-DQA10103-DQB10402	NULL	0.00688		
DRB1_1111	0.00025	NULL		+	HLA-DQA10103-	NULL	0.0107		

Allele	WW freq	Jap freq	*	+	Allele	WW freq	Jap freq	*	+
					DQB10501				
DRB1_1201	0.02325	0.0377	*	+	HLA-DQA10103-DQB10502	NULL	0.00362		+
DRB1_1202	0.0195	0.0181			HLA-DQA10103-DQB10503	NULL	0.00696		
DRB1_1301	0.04575	0.0059		+	HLA-DQA10103-DQB10601	NULL	0.02881		
DRB1_1302	0.0445	0.0595	*	+	HLA-DQA10103-DQB10602	NULL	0.01443		+
DRB1_1303	0.01525	NULL		+	HLA-DQA10103-DQB10603	NULL	0.00134		+
DRB1_1304	0.004	NULL		+	HLA-DQA10103-DQB10604	NULL	0.00938		
DRB1_1305	0.002	NULL			HLA-DQA10103-DQB10609	NULL	0.00046		
DRB1_1307	NULL	0.0001			HLA-DQA10103-DQB10610	NULL	0.00005		+
DRB1_1311	0.00025	NULL		+	HLA-DQA10201-DQB10201	NULL	0.00012		
DRB1_1312	0.001	NULL		+	HLA-DQA10201-DQB10301	NULL	0.00094		
DRB1_1323	0.00025	NULL		+	HLA-DQA10201-DQB10302	NULL	0.00068		
DRB1_1331	0.00025	NULL		+	HLA-DQA10201-DQB10303	NULL	0.00118		
DRB1_1401	0.02275	NULL			HLA-DQA10201-DQB10401	NULL	0.00117		
DRB1_1402	0.00925	0.0006			HLA-DQA10201-DQB10402	NULL	0.00033		
DRB1_1403	0.00125	0.0157			HLA-DQA10201-DQB10501	NULL	0.00051		
DRB1_1404	0.00525	0.0001		+	HLA-DQA10201-DQB10502	NULL	0.00017		
DRB1_1405	0.0045	0.0209			HLA-DQA10201-DQB10503	NULL	0.00033		
DRB1_1406	0.01	0.013		+	HLA-DQA10201-DQB10601	NULL	0.00136		
DRB1_1407	0.001	0.0011			HLA-DQA10201-DQB10602	NULL	0.00068		
DRB1_1412	NULL	0.0003		+	HLA-DQA10201-DQB10603	NULL	0.00006		+
DRB1_1418	0.00025	NULL			HLA-DQA10201-DQB10604	NULL	0.00044		
DRB1_1419	0.00025	NULL		+	HLA-DQA10201-DQB10609	NULL	0.00002		
DRB1_1424	0.00025	NULL		+	HLA-DQA10301-DQB10201	NULL	0.00651		
DRB1_1429	NULL	0.0002			HLA-DQA10301-DQB10301	NULL	0.04949		
DRB1_1445	NULL	0.0001			HLA-DQA10301-DQB10302	0.1	0.03583	*	
DRB1_1454	NULL	0.0327			HLA-DQA10301-DQB10303	NULL	0.06231		
DRB1_1501	0.074	0.0778	*	+	HLA-DQA10301-DQB10401	NULL	0.06205		
DRB1_1502	0.02575	0.1065			HLA-DQA10301-DQB10402	NULL	0.01722		

Allele	WW freq	Jap freq	*	+	Allele	WW freq	Jap freq	*	+
DRB1_1503	0.03125	NULL			HLA-DQA10301-DQB10501	NULL	0.02678		
DRB1_1504	0.00025	0.0001			HLA-DQA10301-DQB10502	NULL	0.00905		
DRB1_1506	0.001	NULL		+	HLA-DQA10301-DQB10503	NULL	0.01743		
DRB1_1601	0.00425	NULL			HLA-DQA10301-DQB10601	NULL	0.07212		
DRB1_1602	0.01725	0.009			HLA-DQA10301-DQB10602	NULL	0.03612		
DRB1_1607	0.00025	NULL			HLA-DQA10301-DQB10603	NULL	0.00334		
DRB3_0101	0.14	NULL	*		HLA-DQA10301-DQB10604	NULL	0.02348		
DRB3_0202	0.189	NULL	*		HLA-DQA10301-DQB10609	NULL	0.00114		
DRB4_0101	0.237	NULL	*		HLA-DQA10301-DQB10610	NULL	0.00013		+
DRB5_0101	0.083	NULL	*		HLA-DQA10401-DQB10201	NULL	0.00048		
HLA-DPA10103-DPB10201	0.092	0.07414	*		HLA-DQA10401-DQB10301	NULL	0.00363		
HLA-DPA10103-DPB10202	NULL	0.00894			HLA-DQA10401-DQB10302	NULL	0.00263		
HLA-DPA10103-DPB10301	0.07	0.01324	*		HLA-DQA10401-DQB10303	NULL	0.00457		
HLA-DPA10103-DPB10401	0.201	0.01953	*		HLA-DQA10401-DQB10401	NULL	0.00455		
HLA-DPA10103-DPB10402	0.236	0.02847	*		HLA-DQA10401-DQB10402	0.066	0.00126	*	
HLA-DPA10103-DPB10501	NULL	0.12313			HLA-DQA10401-DQB10501	NULL	0.00196		
HLA-DPA10103-DPB10601	NULL	0.00265			HLA-DQA10401-DQB10502	NULL	0.00066		
HLA-DPA10103-DPB10801	NULL	0.00066			HLA-DQA10401-DQB10503	NULL	0.00128		
HLA-DPA10103-DPB10901	NULL	0.03608			HLA-DQA10401-DQB10601	NULL	0.00529		
HLA-DPA10103-DPB11001	NULL	0.00033			HLA-DQA10401-DQB10602	NULL	0.00265		
HLA-DPA10103-DPB11301	NULL	0.0053			HLA-DQA10401-DQB10603	NULL	0.00024		
HLA-DPA10103-DPB11401	NULL	0.00629			HLA-DQA10401-DQB10604	NULL	0.00172		
HLA-DPA10103-DPB11601	NULL	0.00132			HLA-DQA10401-DQB10609	NULL	0.00008		
HLA-DPA10103-DPB11701	NULL	0.00033			HLA-DQA10401-DQB10610	NULL	0.00001		+
HLA-DPA10103-DPB11901	NULL	0.00199			HLA-DQA10501-DQB10201	0.058	0.00134	*	
HLA-DPA10201-DPB10101	0.084	NULL	*		HLA-DQA10501-DQB10301	0.195	0.01018	*	
HLA-DPA10201-DPB10201	NULL	0.04032			HLA-DQA10501-DQB10302	NULL	0.00737		
HLA-DPA10201-DPB10202	NULL	0.00486			HLA-DQA10501-DQB10303	NULL	0.01282		
HLA-DPA10201-	NULL	0.0072			HLA-DQA10501-	NULL	0.01276		

Allele	WW freq	Jap freq	*	+	Allele	WW freq	Jap freq	*	+
DPB10301					DQB10401				
HLA-DPA10201-DPB10401	NULL	0.01062			HLA-DQA10501-DQB10402	NULL	0.00354		
HLA-DPA10201-DPB10402	NULL	0.01548			HLA-DQA10501-DQB10501	NULL	0.00551		
HLA-DPA10201-DPB10501	NULL	0.06696			HLA-DQA10501-DQB10502	NULL	0.00186		+
HLA-DPA10201-DPB10601	NULL	0.00144			HLA-DQA10501-DQB10503	NULL	0.00358		
HLA-DPA10201-DPB10801	NULL	0.00036			HLA-DQA10501-DQB10601	NULL	0.01483		
HLA-DPA10201-DPB10901	NULL	0.01962			HLA-DQA10501-DQB10602	NULL	0.00743		
HLA-DPA10201-DPB11001	NULL	0.00018			HLA-DQA10501-DQB10603	NULL	0.00069		
HLA-DPA10201-DPB11301	NULL	0.00288			HLA-DQA10501-DQB10604	NULL	0.00483		
HLA-DPA10201-DPB11401	0.038	0.00342	*		HLA-DQA10501-DQB10609	NULL	0.00023		
HLA-DPA10201-DPB11601	NULL	0.00072			HLA-DQA10501-DQB10610	NULL	0.00003		
HLA-DPA10201-DPB11701	NULL	0.00018			HLA-DQA10601-DQB10201	NULL	0.00048		
HLA-DPA10201-DPB11901	NULL	0.00108			HLA-DQA10601-DQB10301	NULL	0.00363		
HLA-DPA10202-DPB10201	NULL	0.10954			HLA-DQA10601-DQB10302	NULL	0.00263		
HLA-DPA10202-DPB10202	NULL	0.0132			HLA-DQA10601-DQB10303	NULL	0.00457		
HLA-DPA10202-DPB10301	NULL	0.01956			HLA-DQA10601-DQB10401	NULL	0.00455		
HLA-DPA10202-DPB10401	NULL	0.02885			HLA-DQA10601-DQB10402	NULL	0.00126		
HLA-DPA10202-DPB10402	NULL	0.04205			HLA-DQA10601-DQB10501	NULL	0.00196		
HLA-DPA10202-DPB10501	0.115	0.18191	*		HLA-DQA10601-DQB10502	NULL	0.00066		
HLA-DPA10202-DPB10601	NULL	0.00391			HLA-DQA10601-DQB10503	NULL	0.00128		
HLA-DPA10202-DPB10801	NULL	0.00098			HLA-DQA10601-DQB10601	NULL	0.00529		
HLA-DPA10202-DPB10901	NULL	0.0533			HLA-DQA10601-DQB10602	NULL	0.00265		
HLA-DPA10202-DPB11001	NULL	0.00049			HLA-DQA10601-DQB10603	NULL	0.00024		+
HLA-DPA10202-DPB11301	NULL	0.00782			HLA-DQA10601-DQB10604	NULL	0.00172		
HLA-DPA10202-DPB11401	NULL	0.00929			HLA-DQA10601-DQB10609	NULL	0.00008		
HLA-DPA10202-DPB11601	NULL	0.00196			HLA-DQA10601-DQB10610	NULL	0.00001		+
HLA-DPA10202-DPB11701	NULL	0.00049							
HLA-DPA10202-DPB11901	NULL	0.00293							

Table 6a. HLA Class II binding estimates of Cry j 1 peptides

SEQ ID NO:	Allergen	Parent	Pred cover Jap	Pred cover WW	Pred cover Jap 28 HLA's	Pred Cover WW 28 HLA's	Bind cover Jap	Bind cover WW
16	Cha o 1	16	0	0	0	0	0	0
17	Cha o 1	17	0	0	0	0	0	0
18	Cha o 1	18	0	0	0	0	0	0
20	Cha o 1	20	0	0	0	0	0	0
22	Cha o 1	22	0	0	0	0	0	0
23	Cha o 1	23	0	0	0	0	0	0
37	Cry j 1	37	4	14	3	14	0	0
38	Cry j 1	38	82	96	36	96	0	0
39	Cry j 1	39	0	0	0	0	0	0
40	Cry j 1	40	0	0	0	0	0	0
41	Cry j 1	41	1	0	0	0	0	0
42	Cry j 1	42	14	35	2	35	0	0
43	Cry j 1	43	5	35	2	35	0	0
44	Cry j 1	44	0	0	0	0	0	0
45	Cry j 1	45	0	0	0	0	0	0
46	Cry j 1	46	0	16	0	16	0	0
47	Cry j 1	47	0	0	0	0	0	0
48	Cry j 1	48	99	99	80	86	88	97
148	Cry j 1	48	99	99	80	86	0	0
149	Cry j 1	48	99	99	80	86	0	0
49	Cry j 1	49	77	96	47	83	80	95
151	Cry j 1	49	77	96	47	83	0	0
152	Cry j 1	49	77	96	47	83	0	0
50	Cry j 1	50	39	57	37	54	0	0
51	Cry j 1	51	43	47	4	47	28	73
153	Cry j 1	51	63	57	39	55	0	0
52	Cry j 1	52	25	48	7	42	0	0
53	Cry j 1	53	91	98	65	89	80	98
54	Cry j 1	54	90	91	73	81	0	0
55	Cry j 1	55	16	47	4	47	0	0
56	Cry j 1	56	71	74	29	68	68	97
154	Cry j 1	56	72	74	29	68	0	0
155	Cry j 1	56	72	74	29	68	0	0
156	Cry j 1	56	72	74	29	68	0	0
157	Cry j 1	56	71	74	29	68	0	0
57	Cry j 1	57	0	0	0	0	0	0

SEQ ID NO:	Allergen	Parent	Pred cover Jap	Pred cover WW	Pred cover Jap 28 HLA's	Pred Cover WW 28 HLA's	Bind cover Jap	Bind cover WW
5	Cry j 1	58	89	88	78	67	74	80
58	Cry j 1	58	49	77	26	65	0	0
158	Cry j 1	58	89	88	78	67	0	0
159	Cry j 1	58	89	88	78	67	0	0
59	Cry j 1	59	1	0	0	0	0	0
160	Cry j 1	59	1	3	0	0	0	0
161	Cry j 1	59	1	3	0	0	0	0
60	Cry j 1	60	1	0	0	0	0	0
61	Cry j 1	61	11	9	11	8	0	0
62	Cry j 1	62	54	58	15	51	0	0
63	Cry j 1	63	99	99	82	95	79	92
64	Cry j 1	64	3	0	0	0	0	0
162	Cry j 1	64	99	100	82	97	0	0
65	Cry j 1	65	0	26	0	26	0	0
19	Cha o 1	66	44	59	19	55	0	0
6	Cry j 1	66	51	62	29	59	0	0
66	Cry j 1	66	29	57	19	55	48	72
167	Cry j 1	66	69	68	50	65	0	0
168	Cry j 1	66	32	58	19	55	0	0
169	Cry j 1	66	68	68	50	65	0	0
170	Cry j 1	66	67	68	50	65	0	0
171	Cry j 1	66	69	68	50	65	0	0
67	Cry j 1	67	0	0	0	0	0	0
7	Cry j 1	68	85	82	66	67	79	91
68	Cry j 1	68	41	39	2	35	0	0
172	Cry j 1	68	41	43	2	35	0	0
173	Cry j 1	68	41	39	2	35	0	0
69	Cry j 1	69	13	24	12	9	0	0
70	Cry j 1	70	15	35	2	35	0	0
21	Cha o 1	71	17	40	4	39	0	0
15	Cry j 1	71	17	40	4	39	0	0
71	Cry j 1	71	9	35	2	35	0	0
72	Cry j 1	72	8	35	2	35	67	47
174	Cry j 1	72	8	36	2	35	0	0
73	Cry j 1	73	38	74	17	65	0	0
74	Cry j 1	74	18	14	0	0	0	0
75	Cry j 1	75	0	0	0	0	0	0
8	Cry j 1	76	60	59	37	55	0	0

SEQ ID NO:	Allergen	Parent	Pred cover Jap	Pred cover WW	Pred cover Jap 28 HLA's	Pred Cover WW 28 HLA's	Bind cover Jap	Bind cover WW
76	Cry j 1	76	25	11	0	11	57	60
9	Cry j 1	77	95	99	65	98	0	0
77	Cry j 1	77	96	98	69	98	82	94
176	Cry j 1	77	96	99	71	98	0	0
177	Cry j 1	77	96	99	71	98	0	0
178	Cry j 1	77	95	99	65	98	0	0
78	Cry j 1	78	2	35	2	35	0	0
79	Cry j 1	79	0	0	0	0	0	0
80	Cry j 1	80	15	36	2	35	0	0
81	Cry j 1	81	17	51	13	41	24	64
179	Cry j 1	81	84	79	26	71	0	0
181	Cry j 1	81	89	89	30	80	0	0
82	Cry j 1	82	66	67	9	60	65	68
180	Cry j 1	82	73	73	9	67	0	0
150	Cha o 1	150	0	0	0	0	0	0
163	Cha o 1	163	0	0	0	0	0	0
164	Cha o 1	164	0	0	0	0	0	0
165	Cha o 1	165	0	0	0	0	0	0

Table 6b HLA Class II binding estimates of Cry j 2 peptides

SEQ ID NO:	Allergen	Parent	Pred cover Jap(%)	Pred cover WW(%)	Pred cover Jap 28 HLA's(%)	Pred Cover WW 28 HLA's(%)	Bind cover Jap(%)	Bind cover WW(%)
14	Cry j 2	14	96	99	65	95	0	0
30	Cry j 2	30	18	48	13	37	0	0
31	Cha o 2	31	0	0	0	0	0	0
32	Cha o 2	32	0	0	0	0	0	0
33	Cha o 2	33	0	0	0	0	0	0
34	Cha o 2	34	0	0	0	0	0	0
35	Cha o 2	35	0	0	0	0	0	0
36	Cha o 2	36	0	0	0	0	0	0
83	Cry j 2	83	100	100	88	100	0	0
84	Cry j 2	84	95	84	30	82	0	0
85	Cry j 2	85	94	75	11	74	0	0
86	Cry j 2	86	93	96	55	94	0	0

87	Cry j 2	87	100	100	92	99	0	0
88	Cry j 2	88	33	48	12	29	0	0
89	Cry j 2	89	2	0	0	0	0	0
90	Cry j 2	90	0	0	0	0	0	0
91	Cry j 2	91	0	0	0	0	0	0
92	Cry j 2	92	80	47	4	47	27	22
182	Cry j 2	92	92	51	30	51	0	0
183	Cry j 2	92	92	51	30	51	0	0
93	Cry j 2	93	41	59	38	57	0	0
94	Cry j 2	94	82	94	57	76	0	0
95	Cry j 2	95	100	98	57	97	50	80
96	Cry j 2	96	0	0	0	0	0	0
97	Cry j 2	97	98	99	76	94	77	98
184	Cry j 2	97	98	99	76	94	0	0
10	Cry j 2	98	99	99	84	89	0	0
98	Cry j 2	98	91	97	78	88	79	99
185	Cry j 2	98	100	99	84	93	0	0
186	Cry j 2	98	100	99	84	93	0	0
187	Cry j 2	98	99	99	84	89	0	0
188	Cry j 2	98	100	100	84	98	0	0
24	Cry j 2	99	59	90	34	83	0	0
99	Cry j 2	99	59	90	34	83	0	0
25	Cry j 2	100	100	100	80	99	75	95
100	Cry j 2	100	100	100	88	100	89	98
189	Cry j 2	100	100	100	80	99	0	0
190	Cry j 2	100	100	100	80	99	0	0
101	Cry j 2	101	19	46	13	41	0	0
102	Cry j 2	102	0	0	0	0	0	0
103	Cry j 2	103	0	0	0	0	0	0
104	Cry j 2	104	0	0	0	0	0	0
105	Cry j 2	105	0	0	0	0	0	0
191	Cry j 2	105	100	100	88	100	0	0
192	Cry j 2	105	100	100	88	100	0	0
193	Cry j 2	105	100	100	88	100	0	0
26	Cry j 2	106	100	100	88	100	0	0
106	Cry j 2	106	100	100	88	100	70	97
196	Cry j 2	106	100	100	81	99	0	0
197	Cry j 2	106	100	100	81	99	0	0
11	Cry j 2	107	98	99	81	88	0	0
107	Cry j 2	107	98	99	75	90	79	85
194	Cry j 2	107	98	99	81	88	0	0

195	Cry j 2	107	98	99	75	90	0	0
108	Cry j 2	108	1	0	0	0	0	0
109	Cry j 2	109	12	15	2	15	0	0
110	Cry j 2	110	47	73	13	50	0	0
111	Cry j 2	111	0	0	0	0	0	0
27	Cry j 2	112	99	100	84	98	80	96
112	Cry j 2	112	100	100	85	99	0	0
199	Cry j 2	112	100	100	85	99	0	0
200	Cry j 2	112	100	100	85	99	0	0
201	Cry j 2	112	100	100	85	99	0	0
12	Cry j 2	113	77	94	52	86	0	0
113	Cry j 2	113	76	94	52	86	57	82
202	Cry j 2	113	97	100	68	95	0	0
205	Cry j 2	113	77	94	52	86	0	0
206	Cry j 2	113	77	94	52	86	0	0
114	Cry j 2	114	0	0	0	0	0	0
115	Cry j 2	115	52	36	2	35	0	0
116	Cry j 2	116	0	0	0	0	0	0
117	Cry j 2	117	19	35	2	35	0	0
118	Cry j 2	118	3	0	0	0	0	0
13	Cry j 2	119	84	93	63	84	0	0
119	Cry j 2	119	86	93	63	84	82	98
198	Cry j 2	119	99	99	80	91	0	0
203	Cry j 2	119	99	99	80	91	0	0
204	Cry j 2	119	99	99	80	91	0	0
28	Cry j 2	120	78	95	65	86	0	0
120	Cry j 2	120	0	16	0	16	0	0
121	Cry j 2	121	0	0	0	0	0	0
122	Cry j 2	122	57	36	2	35	0	0
123	Cry j 2	123	92	98	52	97	0	0
124	Cry j 2	124	63	93	47	89	0	0
125	Cry j 2	125	80	82	34	80	77	87
207	Cry j 2	125	0	0	0	0	0	0
208	Cry j 2	125	0	0	0	0	0	0
126	Cry j 2	126	29	39	4	39	0	0
127	Cry j 2	127	52	15	2	15	0	0
128	Cry j 2	128	56	57	42	42	0	0
129	Cry j 2	129	95	84	45	81	52	86
209	Cry j 2	129	96	87	51	82	0	0
130	Cry j 2	130	0	0	0	0	0	0
131	Cry j 2	131	0	0	0	0	0	0

29	Cry j 2	132	74	84	57	63	0	0
132	Cry j 2	132	54	85	24	66	0	0
213	Cry j 2	132	92	98	59	94	0	0
133	Cry j 2	133	36	47	4	47	15	37
210	Cry j 2	133	46	47	4	47	0	0
134	Cry j 2	134	0	26	0	26	0	0
135	Cry j 2	135	20	35	2	35	0	0
136	Cry j 2	136	0	16	0	16	0	0
137	Cry j 2	137	0	0	0	0	0	0
138	Cry j 2	138	33	66	7	44	0	0
139	Cry j 2	139	0	16	0	16	0	0
140	Cry j 2	140	43	58	23	35	0	0
141	Cry j 2	141	0	0	0	0	0	0
142	Cry j 2	142	0	0	0	0	0	0
143	Cry j 2	143	76	94	29	82	0	0
144	Cry j 2	144	0	0	0	0	0	0
145	Cry j 2	145	18	42	1	32	0	0
146	Cry j 2	146	25	54	6	40	0	0
212	Cry j 2	212	92	98	59	94	0	0

Example 6. Creation of peptide mixes based on determination of predicted HLA coverage and/or donor T cell response.

Single peptide compositions were designed in order to obtain maximal response in as broad a population as possible. To reach this, peptide compositions were designed to, theoretically, reach the following criteria:

1. Composition must cover both of the major allergens, Cry j 1 and Cry j 2.
2. The composition must have a high HLA population coverage, preferably cover all individuals in a desired population, e.g. worldwide population or Japanese population.
3. The composition must have a large number of HLA binding peptides for each donor (average binding peptides per donor) in order to secure response in each individual.

The peptide compositions were designed using peptides known to have T cell immune response potential, either known from the literature (pool 1 and 2 peptides) or from the T cell screening shown in example 1. In addition, the peptides should have a high probability of being soluble in

aqueous solutions having pH in the range of 4 to 8, as described in Example 2. The design was further guided by high quality in silico HLA binding predictions, in this instant NetMHCIIpan-3.1.

Using HLA peptide binding predictions and knowledge of the frequency of occurrence of each HLA molecule it is possible to theoretically cover a worldwide population using just three peptides (100 % of a population will express at least one HLA molecule predicted to bind at least one of the peptides in the composition.)

To evaluate the compositions, the peptides included were individually tested for T cell response in a relevant cohort of Japanese resident Cedar allergics. For example a 3-peptide mix numbered 242 could be assembled using the peptides with SEQ ID NOs: 48, 97 and 125, wherein a T cell response was found in the following donors:

Donor /Peptide ID	1	2	3	4	5	6	7	8	9	10
48	x	x	x		x		x		x	
97				x	x	x	x		x	x
125						x		x		

The compositions were evaluated on the following measures A to N:

A) T cell response coverage

This is simply how large a fraction that will respond to at least one peptide in the composition. For mix 242 this is 100% as seen from table 7a.

B) Responding peptides per donor

This express how many peptides, on average, each donor will react to. As seen in above for Mix 242, each donor react against one or two peptides, thus the measure is the simple average $(1+1+1+1+2+2+2+1+2+1)/10 = 1.4$

C) Predicted HLA Coverage worldwide population

The predicted HLA coverage of a peptide composition is determined by the total set of HLA molecules predicted to bind to any of the peptides in a composition using the set of alleles of a worldwide population shown in Table 5. (see also G, HLA binding coverage)

D) Predicted HLA Coverage Japanese Population

The predicted HLA coverage of a peptide composition is determined by the set of HLA molecules predicted to bind to any of the peptides in a composition using the set of alleles of a Japanese population shown in Table 5.

5 E) Predicted HLA Coverage worldwide population (28 HLA alleles)

Same as for C), but only estimated with the use of the set of 28 HLA alleles used for binding assay (indicated by asterisk in Table 5).

F) Predicted HLA Coverage Japanese Population (28 HLA alleleles)

10 Same as for D), but only estimated with the use of the set of 28 HLA alleles used for binding assay (indicated by asterisk in Table 5).

G) HLA binding coverage in a worldwide population

The HLA binding coverage of a peptide composition is calculated from the total set of HLAs that bind to any peptide in the composition in an experimental binding assay. Table 4 in the binding section shows which HLAs that bind the peptides included in Mix242. This peptides in Mix242 binds to the DRB1 molecules DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*09:01, DRB1*11:01, DRB1*13:02, and DRB1*15:01, the DRB3_0101, DRB3_0202, DRB4_0101, DRB5_0101, the HLA-DP molecules DPB1_0201, DPB1_0401, DPB1_0402, DPB1_0501, and DPB1_1401 but none of the HLA-DQ molecules. Using the allele frequencies of table 5 for a worldwide population the HLA coverage is calculated as described in example 9 for a single peptide. Thus here the DRB1 locus allele sum will be $(0.04275 + 0.07725 + 0.03375 + 0.02325 + 0.1015 + 0.02725 + 0.0395 + 0.057 + 0.0445 + 0.074) = 0.5208$. The DRB1 locus Coverage is then $(0.5208 \times 2) - 0.5208^2 = 0.77$.

25 The DRB3 allele sum is $(0.14 + 0.189) = 0.329$. The DRB3 Locus Coverage is then $(0.329 \times 2) - 0.329^2 = 0.5498$. the DRB4 locus coverage is $(0.237 \times 2) - 0.237^2 = 0.4178$. the DRB5 locus coverage is $(0.083 \times 2) - 0.083^2 = 0.1591$. the DP allele frequency sum is $(0.092 + 0.201 + 0.236 + 0.115 + 0.038) = 0.682$ and the DP locus coverage is $(0.682 \times 2) - 0.682^2 = 0.8989$. As no DQ molecules bind any of the peptides in Mix242 the HLA-DQ locus coverage is 0.

Like in example 4, binding coverage;

$$\begin{aligned}
 K0 &= 0, \\
 30 \quad K1 &= K0 + (1 - K0) \times C1 = 0 + (1 - 0) \times 0.77 &= 0.77 \\
 K2 &= K1 + (1 - K1) \times C2 = 0.77 + (1 - 0.77) \times 0.5498 &= 0.896 \\
 K3 &= K2 + (1 - K2) \times C3 = 0.896 + (1 - 0.896) \times 0.418 &= 0.939 \\
 K4 &= K3 + (1 - K3) \times C4 = 0.939 + (1 - 0.939) \times 0.1591 &= 0.949
 \end{aligned}$$

$$K5 = K4 + (1 - K4) \times C5 = 0.949 + (1 - 0.949) \times 0.8989 = 0.995$$

$$K6 = K5 + (1 - K5) \times C6 = 0.995 + (1 - 0.995) \times 0 = 0.995$$

= 99.5% predicted HLA coverage in a worldwide population.

H) HLA binding coverage in a Japanese population

5 Same as for G) but estimated for a Japanese population.

I) Predicted Average Peptide bind per donor in a worldwide population

To estimate the predicted peptide binding valency of the peptide combinations disclosed herein, a system was created that generates virtual patients (VP). The population in this case is a theoretical in silico population of 10000 VPs. Each VP was generated using the 80 allele frequencies for a worldwide population from table 5 as probabilities at each locus to have this particular allele. For the DRB1 locus we have full knowledge of allele distribution in the considered populations, and the allele frequencies will sum up to 1.0. However, for DRB 3, 4 and 5 not all individuals express an allele at the given locus, and for the DQ and DP loci we do not have full knowledge of the allele distributions, thus the used allele frequencies for these loci will not sum up to one. Consequently, some of the generated VPs would lack one or both alleles at these loci. As a result the calculated theoretical population coverage will be under-estimated, but will serve as a good guidance. To estimate the average fraction of patients reacting against a certain number of peptides, 10000 VPs were generated. Using the prediction method and affinity thresholds (300 nM and 30% fractile) described in Example 5, the number of peptides that each VP would potentially bind in the peptide combinations disclosed herein was predicted, and the simple mean of all numbers calculated as for B).

J) Predicted Average Peptide bind per donor in a Japanese population

As above for I) but using the 160 frequencies for a Japanese population.

K) Predicted Average Peptide bind per donor in a worldwide population (28 HLA alleles)

25 As above for I) using worldwide HLA frequencies but limited to the panel of 28 alleles in the binding panel.

L) Predicted Average Peptide bind per donor in a Japanese population (28 HLA alleles)

As above for I) using Japanese HLA frequencies but limited to the 23 alleles in the binding panel found in a Japanese population.

30 M) Binding Average Peptide per donor in a worldwide population (26 HLA alleles)

This expresses the average number of binding peptides per individual in a population. The binding is based on data from in vitro HLA class II binding assays using a selection of HLA class II alleles, in

the present example performed as described in Example 4 and using the 26 alleles listed in Table 4. However, other suitable methods for measuring HLA Class II binding and other sets of HLA class II alleles could also be used. The population in this example is simulated by generating virtual patients VPs using the selection of HLA Class II alleles of Table 4 and the corresponding HLA frequencies in a worldwide population from table 5 as described under I).

N) Binding Average Peptide per donor in a Japanese population ((26 HLA alleles)

As above but using the Japanese HLA frequencies in Table 5.

Resulting Mixes

Table 7a. Mixes comprising 3 peptides and variant mixes thereof (mix 242 through mix 236).

SEQ ID NO:	242	242a	243	243a	243b	273	273a	273b	240	240a	246	246a	246b	236	236a	236b
48	X		x								x					
148		x		x	x							x	x			
56											x					
155												x				
156																
157													x			
66														x		
167															x	
170																x
77						x			x		x					
176							x	X		x		x	x			
97	X		x			x			x					x		
184		x		x	x		x	X		x					x	x
107			x			x										
194				x			x									
195					x			x								
125	X								x					x		
208		x								x					x	

- 10 Table 7a-continued Preferred mixes comprising 3 peptides and variant mixes thereof (mix 238 through mix 244).

SEQ ID NO:	238	238a	238b	238c	238d	241	241a	241b	245	244
56						x			x	
154										
155							x			
157								x		
66	X									

SEQ ID NO:	238	238a	238b	238c	238d	241	241a	241b	245	244
167		x		X						
170			x		x					
77	X								x	X
176		x		X						
97						x				
184							x	x		
107	X								x	X
194		X	x							
195				X	x					
125						x				X
208							x	x		

Table 7b. T-cell donor and HLA coverage of 3- mixes (mix 242 through 244)

Mix number/ Measure	242	243	273	240	246	236	238	241	245	244
A(%)	100	90	90	90	80	80	80	80	80	80
B	1.4	1.5	1.4	1.3	1.4	1.2	1.2	1.1	1.1	1
C(%)	100	100	100	100	100	100	100	100	100	100
D(%)	100	100	100	100	100	99	100	99	100	100
E(%)	99	98	100	100	99	98	99	98	99	99
F(%)	85	81	86	81	85	80	86	80	86	86
G	2.79	2.95	2.96	2.79	2.71	2.38	2.55	2.55	2.71	2.79
H	2.77	2.95	2.93	2.75	2.67	2.09	2.24	2.51	2.66	2.75
I	2.61	2.7	2.82	2.72	2.53	2.29	2.43	2.43	2.57	2.68
J	1.89	2.3	2.18	1.78	1.77	1.3	1.63	1.39	1.72	1.77
K(%)	100	100	100	100	100	100	100	100	100	100
L(%)	92	90	93	95	99	100	100	94	98	94
M	2.83	2.81	2.77	2.79	2.88	2.57	2.51	2.82	2.76	2.66
N	2.4	2.41	2.35	2.34	2.36	2.02	2.08	2.2	2.26	2.36

Table 8a. Mixes comprising 4 peptides and variant mixes thereof (mix 253 through mix 248b).

SEQ ID NO:	253	253a	253b	247	247a	247b	293	293a	293b	293c	293d	251	251a	251b	248	248a	248b
48	x																
148		x	X														
56							x					x					

SEQ ID NO:	253	253a	253b	247	247a	247b	293	293a	293b	293c	293d	251	251a	251b	248	248a	248b
154																	
155								x		x			x				
156														X			
157									x		x						
66				x											x		
6																	
167					x											x	
170						x											x
166																	
77				x			X					x			x		
176					x	x		x	x	x	x		x	x		x	
97	x			x			X					x					
184		x	x		x	x		x	x	x	x		x	x			
107	x						X								x		
11																	
194		x						x	x							x	x
195			x							x	x						
125	x			x								x			x		
208		x	x		x	x							x	x		x	x

Table 8a-continued Mixes comprising 4 peptides and variant mixes thereof (mix 248c through mix 249).

SEQ ID NO:	248c	248d	252	252a	252b	252c	252d	254	250	255	249
48									x	x	
56			X					x	x	x	x
155				x		x					
156											
157					X		x				
66									x		x
167	x										
170		x									
77								x	x	x	x
176	x										
97			X								
184				x	x	x	x				

SEQ ID NO:	248c	248d	252	252a	252b	252c	252d	254	250	255	249
107			X					x		x	x
194		x		x	x						
195	X	x				x	x				
125			X					x			
208	X	x		x	x	x	x				

Table 8b. T-cell donor and HLA coverage of preferred 4- mixes (mix 253 through 249)

Mix number/ Measure	253	247	293	251	248	252	254	250	255	249
A(%)	100	90	90	90	90	90	90	80	80	80
B	1.7	1.7	1.7	1.6	1.4	1.4	1.3	1.8	1.7	1.5
C(%)	100	100	100	100	100	100	100	100	100	100
D(%)	100	100	100	100	100	100	100	100	100	100
E(%)	99	100	100	100	99	99	99	99	100	99
F(%)	85	81	86	81	86	85	86	85	86	86
G	3.77	3.37	3.7	3.53	3.37	3.53	3.53	3.29	3.7	3.29
H	3.76	3.05	3.65	3.47	3.05	3.49	3.47	2.97	3.65	2.97
I	3.5	3.27	3.51	3.41	3.24	3.33	3.37	3.08	3.43	3.12
J	2.64	1.98	2.47	2.07	1.97	2.14	2.06	1.97	2.51	1.92
K(%)	71	98	85	88	98	63	86	100	96	99
L(%)	100	100	100	100	100	100	100	100	100	100
M	3.18	2.83	3.02	3.02	2.85	2.98	3.04	2.85	3.14	2.75
N	3.68	3.5	3.75	3.76	3.37	3.68	3.63	3.59	3.73	3.48

Table 9a Mixes comprising 5 peptides and variant mixes thereof (mix 153 through 261d).

SEQ ID NO:	153	153a	153b	256	256a	256b	259	259a	259b	259c	259d	261	261a	261b	261c	261d
48	x											x				
148		x	x										x	x	x	x
56	x						x					x				
155									x	x			x			x
157		x	x				X	x					x		x	
66				x												
167						x										
170					x											
77				x			x					x				
176					x	x		X	x	x	x		x	x	x	x

SEQ ID NO:	153	153a	153b	256	256a	256b	259	259a	259b	259c	259d	261	261a	261b	261c	261d
97	x			x			x									
184		x	x		x	x		X	x	x	x					
107	x			x			x					x				
194		x			x	x		X		x			x	x		
195			x						x		x				x	x
125	x			x			x					x				
208		x	x		x	x		X	x	x	x					

Table 9b. T-cell donor and HLA coverage of 5- mixes (mixes 153 thorough 261)

Mix number/ Measure	153	256	259	261
A(%)	100	100	100	90
B	2	2	1.9	1.9
C(%)	100	100	100	100
D(%)	100	100	100	100
E(%)	99	100	100	100
F(%)	85	86	86	86
G	4.52	4.35	4.52	4.52
H	4.48	4.03	4.45	4.45
I	4.19	4.17	4.31	4.23
J	2.93	2.73	2.82	2.86
K(%)	100	100	100	100
L(%)	69	93	70	94
M	4.65	4.36	4.61	4.6
N	3.85	3.61	3.79	3.91

Table 10a. Mixes comprising 6 peptides and variant mixes thereof (mixes 263 through 262d).

SEQ ID NO:	263	263a	263b	267	267a	267b	267c	267d	264	264a	264b	264c	264d	265	265a	265b	265c	265d	262	262a	262b	262c	262d
48	X			x					x					x									
148		x	x		x	x	x	x		x	X	x	x		x	x	x	x					
56				x					x					x					x				
155						x		x				x	x								x		x
156																							
157					x		x			x	X									x	x		
66	X			x										x					x				
167			x				x	x									x	x			x		x
170		x			x	x									x	x				x		x	

SEQ ID NO:	263	263a	263b	267	267a	267b	267c	267d	264	264a	264b	264c	264d	265	265a	265b	265c	265d	262	262a	262b	262c	262d
166																							
77	X			x					x										x				
176		x	x		x	x	x	x		x	X	x	x							x	x	x	x
97	X			x					x					x					x				
184		x	x		x	x	x	x		X	X	x	x		x	x	x	x		x	x	x	x
107	X								x					x					x				
11																							
194		x	x							X		x			x		x			x	x	x	x
195											X		x			x		x					
125	X			x					x					x					x				
208		x	x		x	x	x	x		X	X	x	x		x	x	x	x		x	x	x	x

Table 10b. T-cell donor and HLA coverage of 6-mixes (mix 263 through mix 262)

Mix number/ Measure	263	267	264	265	262
A(%)	100	100	100	100	100
B	2.6	2.6	2.5	2.4	2.3
C(%)	100	100	100	100	100
D(%)	100	100	100	100	100
E(%)	100	100	100	99	100
F(%)	86	86	86	85	86
G	5.33	5.09	5.5	5.09	5.1
H	5.02	4.76	5.44	4.78	4.75
I	5.04	4.82	5.17	4.74	4.86
J	3.52	3.07	3.61	3.14	3.02
K(%)	100	98	94	96	96
L(%)	100	100	100	100	100
M	4.48	4.38	4.67	4.34	4.28
N	5.33	5.45	5.59	5.37	5.33

Table 11a. Additional mixes comprising either 3, 4, 5 or 6 Cry j 1 and Cry j 2 peptides (mixes 282 through mix 340)

		Mix size	3	3	3	4	4	4	4	4	5	5
SEQ ID NO:	Allergen	parent SEQ ID NO:	282	277	281	297	301	302	295	299	316	320

14	Cry j 2	14						x				
17	Cha o 1	49									x	x
56	Cry j 1	56	x		x	x	x	x	x	x		
77	Cry j 1	77	x	x	x	x	x	x				
10	Cry j 2	98	x				x	x			x	x
25	Cry j 2	100		x	x	x	x		x	x	x	x
107	Cry j 2	107		x		x			x	x	x	x
125	Cry j 2	125							x	x	x	x

Table 11a-continued. Additional mixes comprising either 3, 4, 5 or 6 Cry j 1 and Cry j 2 peptides (mixes 282 through mix 340)

		Mix size	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6
SEQ ID NO:	Allergen	parent SEQ ID NO:	313	313a	313b	313c	315	315a	315b	315c	315d	315e	315f	335	336	340	335a	335b	335c	335d	335e	335f	
17	Cha o 1	49					x	x	x	x	315d	315e	315f	x	x	x	x	x	x				
49	Cry j 1	49																		x	x	x	
56	Cry j 1	56	x				x							x									
154	Cry j 1	56		x				x			x						x			x			
155	Cry j 1	56			x				x			x						x			x		
156	Cry j 1	56				x				x			x						x			x	
18	Cha o 1	64													x	x							
77	Cry j 1	77	x																				
176	Cry j 1	77		x	x	x																	
97	Cry j 2	97	x																				
184	Cry j 2	97		x	x	x																	
10	Cry j 2	98												x	x	x							
185	Cry j 2	98															x	x	x	x	x	x	
25	Cry j 2	100	x				x							x	x	x							
189	Cry j 2	100		x	x	x		x	x	x	x	x	x				x	x	x	x	x	x	
107	Cry j 2	107	x				x							x	x	x							
11	Cry j 2	107		x	x	x		x	x	x	x	x	x				x	x	x	x	x	x	
125	Cry j 2	125					x							x	x	x							
208	Cry j 2	125						x	x	x	x	x	x				x	x	x	x	x	x	

- 5 Table 11.b T-cell donor and HLA coverage of other preferred 3, 4, 5 and 6- mixes (mixes 282 through 340)

Mix / Measure	282	277	281	297	301	302	295	299	313	316	320	315	335	336	340
A(%)	80	80	80	90	80	80	80	80	90	90	90	80	100	90	90

B	1.5	1.2	1.2	1.5	1.9	1.5	1.2	1.2	2.1	1.6	1.6	1.2	1.9	1.6	1.6
C(%)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
D(%)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
E(%)	99	100	100	100	100	100	100	100	100	100	100	100	100	100	100
F(%)	88	91	91	91	93	92	91	91	91	93	93	91	93	93	93
G	2.72	2.97	2.73	3.71	3.72	3.71	3.55	3.55	4.7	3.79	3.79	3.55	4.54	3.79	3.79
H	2.67	2.94	2.68	3.66	3.67	3.63	3.51	3.51	4.65	3.78	3.78	3.51	4.5	3.78	3.78
I	2.56	2.87	2.66	3.56	3.55	3.5	3.39	3.39	4.5	3.59	3.59	3.39	4.28	3.59	3.59
J	1.8	2.23	1.78	2.52	2.6	2.45	2.19	2.19	3.28	2.72	2.72	2.19	3.01	2.72	2.72
K(%)	N/A	100	100	100	N/A	N/A	100	100	100	N/A	N/A	N/A	N/A	N/A	N/A
L(%)	N/A	98	100	96	N/A	N/A	86	86	90	N/A	N/A	N/A	N/A	N/A	N/A
M	N/A	2.75	2.86	3.72	N/A	N/A	3.65	3.65	4.7	N/A	N/A	N/A	N/A	N/A	N/A
N	N/A	2.33	2.23	3.01	N/A	N/A	2.96	2.96	3.76	N/A	N/A	N/A	N/A	N/A	N/A

Further mixes

Furhter 55 different mixes are suggested, using either the 32 peptides of SEQ ID Nos. 5-36 or the 16-mer peptides of SEQ ID Nos. 37-146. These mixes show a high estimated HLA Class II coverage in which all individuals in a worldwide population are predicted to have HLA alleles from, wherein at least two different loci are predicted to bind to at least one of the peptides in a given mix. Such mixes enhance the likelihood that any given individual will contain an appropriate T cell receptor for recognition of the MHC:peptide complex, and will generally increase the theoretical maximal possible concentration of peptide-loaded MHC molecules.

- 10 Using the allele frequencies shown in Table 5 and the theoretical population of 10000 individuals as described in example 4, further mixes of five peptides were designed to be able to bind, on average, to a maximum number of MHCs per individual in the theoretical population. For each of these mixes it was determined how many of the HLAs present in a given haplotype are predicted to bind to at least one of the peptides in the given mix of five peptides. The mixes were selected from
- 15 either the 32 peptides of SEQ ID Nos. 5-36 ("pool 32" mixes) or from the peptides of SEQ ID Nos. 37-146 ("16-mer" mixes).

The following 30 mixes of 5 peptides each were designed using the 16-mer peptides of SEQ ID Nos. 37-146:

- 16-mer mix 0.0: SEQ ID NOs: 106, 63, 77, 112, 53

- 16-mer mix 0.1: SEQ ID NOs: 106, 63, 87, 56, 85
- 16-mer mix 0.2: SEQ ID NOs: 106, 63, 100, 49, 124
- 16-mer mix 0.3: SEQ ID NOs: 106, 63, 113, 62, 123
- 16-mer mix 0.4: SEQ ID NOs: 106, 63, 107, 59, 68
- 5 • 16-mer mix 1.0: SEQ ID NOs: 100, 77, 53, 123, 85
- 16-mer mix 1.1: SEQ ID NOs: 100, 77, 119, 49, 124
- 16-mer mix 1.2: SEQ ID NOs: 100, 77, 110, 48, 84
- 16-mer mix 1.3: SEQ ID NOs: 100, 77, 97, 107, 73
- 16-mer mix 1.4: SEQ ID NOs: 100, 77, 98, 59, 129
- 10 • 16-mer mix 2.0: SEQ ID NOs: 112, 53, 123, 56, 95
- 16-mer mix 2.1: SEQ ID NOs: 112, 53, 124, 85, 62
- 16-mer mix 2.2: SEQ ID NOs: 112, 53, 107, 87, 81
- 16-mer mix 2.3: SEQ ID NOs: 112, 53, 84, 97, 59
- 16-mer mix 2.4: SEQ ID NOs: 112, 53, 119, 52, 48
- 15 • 16-mer mix 3.0: SEQ ID NOs: 87, 49, 85, 48, 123
- 16-mer mix 3.1: SEQ ID NOs: 87, 49, 119, 62, 56
- 16-mer mix 3.2: SEQ ID NOs: 87, 49, 107, 97, 73
- 16-mer mix 3.3: SEQ ID NOs: 87, 49, 124, 129, 95
- 16-mer mix 3.4: SEQ ID NOs: 87, 49, 110, 84, 58
- 20 • 16-mer mix 4.0: SEQ ID NOs: 123, 119, 48, 95, 56
- 16-mer mix 4.1: SEQ ID NOs: 123, 119, 73, 62, 107
- 16-mer mix 4.2: SEQ ID NOs: 123, 119, 58, 125, 52
- 16-mer mix 4.3: SEQ ID NOs: 123, 119, 81, 59, 85
- 16-mer mix 4.4: SEQ ID NOs: 123, 119, 82, 64, 84
- 25 • 16-mer mix 5.0: SEQ ID NOs: 107, 48, 124, 95, 85
- 16-mer mix 5.1: SEQ ID NOs: 107, 48, 97, 56, 125
- 16-mer mix 5.2: SEQ ID NOs: 107, 48, 110, 62, 59
- 16-mer mix 5.3: SEQ ID NOs: 107, 48, 132, 129, 52

Similarly, the following 25 mixes of 5 peptides each were designed using the peptides of SEQ ID

30 NOs: 5-36:

- pool 32 mix 0.0: SEQ ID NOs: 5, 9, 18, 26, 27
- pool 32 mix 0.1: SEQ ID NOs: 7, 9, 25, 26, 31
- pool 32 mix 0.2: SEQ ID NOs: 9, 12, 14, 17, 26
- pool 32 mix 0.3: SEQ ID NOs: 9, 13, 16, 26, 35
- 35 • pool 32 mix 0.4: SEQ ID NOs: 8, 9, 11, 26, 32
- pool 32 mix 1.0: SEQ ID NOs: 7, 18, 25, 28, 31
- pool 32 mix 1.1: SEQ ID NOs: 5, 13, 18, 25, 27

- pool 32 mix 1.2: SEQ ID NOs: 10, 14, 15, 18, 21, 25
- pool 32 mix 1.3: SEQ ID NOs: 8, 12, 18, 25, 30
- pool 32 mix 1.4: SEQ ID NOs: 6, 11, 18, 25, 35
- pool 32 mix 2.0: SEQ ID NOs: 5, 8, 13, 14, 27
- 5 • pool 32 mix 2.1: SEQ ID NOs: 5, 7, 27, 28, 31
- pool 32 mix 2.2: SEQ ID NOs: 5, 10, 15, 21, 27, 35
- pool 32 mix 2.3: SEQ ID NOs: 5, 17, 24, 27, 32
- pool 32 mix 2.4: SEQ ID NOs: 5, 16, 27, 30, 33
- pool 32 mix 3.0: SEQ ID NOs: 7, 8, 13, 14, 31
- 10 • pool 32 mix 3.1: SEQ ID NOs: 7, 10, 14, 17, 24
- pool 32 mix 3.2: SEQ ID NOs: 7, 11, 14, 28, 35
- pool 32 mix 3.3: SEQ ID NOs: 7, 12, 14, 16, 32
- pool 32 mix 3.4: SEQ ID NOs: 7, 14, 29, 30, 33
- pool 32 mix 4.0: SEQ ID NOs: 8, 12, 13, 15, 21, 31
- 15 • pool 32 mix 4.1: SEQ ID NOs: 8, 10, 13, 17, 28
- pool 32 mix 4.2: SEQ ID NOs: 8, 11, 13, 16, 35
- pool 32 mix 4.3: SEQ ID NOs: 6, 8, 13, 20, 32
- pool 32 mix 4.4: SEQ ID NOs: 8, 13, 19, 29, 33

Measures A to N to estimate the HLA class II coverage may be determined as described in the
 20 present example.

CLAIMS

1. A composition comprising three peptides, which independently are 13 to 25
 5 amino acid residues in length, wherein
- a peptide of formula I has an amino acid sequence defined by: a-A1-C1-B1-b
 - a peptide of formula I* has an amino acid sequence defined by: a-A1-C1*-B1-b
 - a peptide of formula II has an amino acid sequence defined by: a-A2-C2-B2-b
 - a peptide of formula II* has an amino acid sequence defined by: a-A2-C2*-B2-b
- 10 which composition comprises a first peptide selected from peptides of formula I and I*,
 wherein
- C1 in formula I is an amino acid sequence of SEQ ID NO: 48,
 C1* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined
 15 in C1 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2
 substitutions if C1* is shorter than C1,
- a second peptide selected from peptides of formula II and II*, wherein
- C2 in formula II is an amino acid sequence of SEQ ID NO: 97,
 C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined
 20 in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2
 substitutions if C2* is shorter than C2, and
- a third peptide selected from peptides of formula II and II*, wherein
- C2 in formula II is an amino acid sequence of SEQ ID NO: 107,
 C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined
 25 in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2
 substitutions if C2* is shorter than C2;
- A1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal
 amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue
 substitutions;

- B1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- A2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- B2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

and wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

15

2. A composition comprising three peptides, which independently are 13 to 25 amino acid residues in length, wherein a first peptide is selected from group a) comprising peptides of either formula I or I*, a second peptide is selected from group b) comprising peptides of either formula II or II* and a third peptide is selected from group c) comprising peptides of group a) and b), wherein

20

- a peptide of formula I has an amino acid sequence defined by: a-A1-C1-B1-b
- a peptide of formula I* has an amino acid sequence defined by: a-A1-C1*-B1-b
- a peptide of formula II has an amino acid sequence defined by: a-A2-C2-B2-b
- a peptide of formula II* has an amino acid sequence defined by: a-A2-C2*-B2-b

25

and wherein

- C1 is an amino acid sequence selected from any one of SEQ ID NOs: 77, 48, 56 and 66,
- C1* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C1 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C1* is shorter than C1;
- C2 is an amino acid sequence selected from any one of SEQ ID NOs: 97, 107 and 125;
- C2* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C2 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C2* is shorter than C2;
- A1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;

30

35

- B1 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;
- A2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- B2 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;
- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

and wherein C1, C1*, C2, or C2* in the third peptide is neither identical to, nor defined from, the same SEQ ID NO as C1 in the first peptide or C2 in the second peptide.

15

3. The compositions according to claim 1, wherein the only substitution(s) in C1*, C2*, A1, A2, B1 and B2 is cysteine substituted with serine.
4. The composition according to any one of the preceding claims, comprising three peptides having an amino acid sequence as defined for peptide mixes numbered 243, 243a, 243b in Table 7a.
5. The composition according to any one of the preceding claims insofar as they depend on claim 2 comprising a fourth, fifth, sixth and/or further peptide independently selected from peptides of formula I, II, I* and II*, wherein
- 25 C1 in formula I is an amino acid sequence selected from SEQ ID NOs: 56, 66 and 77, C1* in formula I* is either a fragment of SEQ ID NOs: 56, 66 or 77 with 0, 1, or 2 amino acid substitutions compared to a fragment of SEQ ID NOs: 56, 66 or 77 of the same length, or SEQ ID NOs: 48, 56, 66 or 77 with 1 or 2 amino acid substitutions,
- C2 in formula II is an amino acid sequence of SEQ ID NO: 125,
- 30 C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid substitutions compared to a fragment of SEQ ID NO: 125 of the same length, or SEQ ID NO 125 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

6. The composition according to any one of the preceding claims insofar as they depend on claim 2, comprising four peptides as defined in any one of the peptide mixes numbered 253, 253a, 253b, in Table 8a.

7. The composition according to any one of the preceding claims insofar as they
5 depend on claim 2, comprising a first peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 48,
C1* in formula I* is either a fragment of SEQ ID NO: 48 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NO: 48 of the same length, or SEQ ID NO: 48
10 with 1 or 2 amino acid substitutions,

a second peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 97,
C2* in formula II* is either a fragment of SEQ ID NO: 97 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NO: 97 of the same length, or SEQ ID NO: 97
15 with 1 or 2 amino acid substitutions,

a third peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 107,
C2* in formula II* is either a fragment of SEQ ID NO: 107 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NO: 107 of the same length, or SEQ ID NO: 107
20 with 1 or 2 amino acid substitutions;

a fourth peptide selected from peptides of formula II and II*, wherein

C2 in formula II is an amino acid sequence of SEQ ID NO: 125,
C2* in formula II* is either a fragment of SEQ ID NO: 125 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NO: 125 of the same length, or SEQ ID NO: 125
25 with 1 or 2 amino acid substitutions; and

a fifth peptide selected from peptides of formula I and I*, wherein

C1 in formula I is an amino acid sequence of SEQ ID NO: 56,
C1* in formula II* is either a fragment of SEQ ID NO: 56 with 0, 1, or 2 amino acid
substitutions compared to a fragment SEQ ID NO: 56 of the same length, or SEQ ID NO: 56
30 with 1 or 2 amino acid substitutions,

wherein C1, C1*, C2, or C2* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO C1 or C2 as any other peptide in the composition.

8. The composition according to any one of the preceding claims insofar as they depend on claim 2, comprising five peptides as defined in any one of the peptide mixes
5 numbered 153, 153a, 153b, as shown in Table 9a.

9. The composition according to any one of the preceding claims insofar as they depend on claim 2 comprising a fourth, fifth, sixth and/or further peptide, which peptide(s) independently are 13 to 25 amino acid residues in length, wherein any one of the fourth, fifth, sixth or further peptide is of either formula III or III* or formula IV or IV*, wherein

- 10 - a peptide of formula III has an amino acid sequence defined by: a-A3-C3-B3-b
- a peptide of formula III* has an amino acid sequence defined by: a-A3-C3*-B3-b
- a peptide of formula IV has an amino acid sequence defined by: a-A4-C4-B4-b
- a peptide of formula IV* has an amino acid sequence defined by: a-A4-C4*-B4-b

and wherein

15 C3 is an amino acid sequence selected from any one of SEQ ID NOs: 49, 59, or 64,

C3* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C3 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C3* is shorter than C3;

C4 is an amino acid sequence selected from any one of SEQ ID NOs: 14, 98, 100 or 113,

20 C4* consists of 13 to 16 contiguous amino acid residues of the amino acid sequence defined in C4 with either 1, 2 or 3 amino acid residue substitutions or with either 0, 1 or 2 substitutions if C4* is shorter than C4;

- A3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue
25 substitutions;

- B3 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C1 in SEQ ID NO: 1, including 0, 1 or 2 amino acid residue substitutions;

- A4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the N-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;

5 - B4 is an amino acid sequence of 0-6 contiguous amino acid residues flanking the C-terminal amino acid residue of C2 in SEQ ID NO: 3, including 0, 1 or 2 amino acid residue substitutions;

- a and b is independently 0, 1, 2 or 3 amino acid residues selected among the amino acids lysine (K), arginine (R), aspartic acid (D) and glutamic acid (E);

10 and wherein C3, C3*, C4, or C4* in any of the peptides in the composition is neither identical to, nor defined from, the same SEQ ID NO as C1, C2, C3 or C4 as any other peptide in the composition.

10. The compositions according to claim 9, wherein the only substitution(s) in C3*, C4*, A3, A4, B3 and B4 is cysteine substituted with serine.

11. The composition according to any one of the preceding claims insofar as they
15 depend on claim 2 comprising at least 4, 5, 6, 7 or 8 peptides.

12. The composition according to any one of the preceding claims insofar as they depend on claim 2 comprising at the most 4, 5, 6, 7 or 8 peptides.

13. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the peptides of the composition in combination bind at least 18
20 of 26 HLA Class II molecules selected from the group consisting of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405,
25 DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101, DRB5_0101, such as at least 19, 20, 21, 22, 23, 24, 25 or 27 of said HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

14. The composition according to any one of the preceding claims insofar as they
30 depend on claim 2, wherein the peptides of the composition in combination bind at least 70% of the HLA Class II molecules of Table 5, column 3, such as at least 75%, 80%, 84%, 88%,

90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules, when binding is determined by in vitro or in silico test conditions.

15. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein any of the amino acid sequences of the C1* and C2* in the composition binds at least 70% of the HLA Class II molecules that C1 and C2 binds, respectively, such as binds at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that C1 and C2 binds, respectively, when binding is determined by similar in vitro or in silico test conditions.
16. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein any of the amino acid sequence(s) of a peptide of formula I or I* binds at least 70% of the HLA Class II molecules that the respective C1 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C1 binds, when binding is determined by similar in vitro or in silico test conditions.
17. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid sequence of a peptide(s) of formula II or II* binds at least 70% of the HLA Class II molecules that the respective C2 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C2 binds, when binding is determined by similar in vitro or in silico test conditions.
18. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid sequence of a peptide(s) of formula III or III* binds at least 70% of the HLA Class II molecules that the respective C3 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C3 binds, when binding is determined by similar in vitro or in silico test conditions.
19. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid sequence of a peptide(s) of formula IV or IV* binds at least 70% of the HLA Class II molecules that the respective C4 binds, such as bind at least 75%, 80%, 84%, 88%, 90%, 92%, 94% 96%, 98% of said group of HLA Class II molecules that the respective C4 binds, when binding is determined by similar in vitro or in silico test conditions.

20. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the group of HLA Class II molecules consists of HLA-DPA10103-DPB10201, HLA-DPA10103-DPB10301, HLA-DPA10103-DPB10401, HLA-DPA10103-DPB10402, HLA-DPA10202-DPB10501, HLA-DPA10201-DPB11401, HLA-DQA10501-DQB10201, HLA-DQA10501-DQB10301, HLA-DQA10301-DQB10302, HLA-DQA10101-DQB10501, HLA-DQA10102-DQB10602, DRB1_0101, DRB1_0301, DRB1_0401, DRB1_0405, DRB1_0701, DRB1_0802, DRB1_0901, DRB1_1101, DRB1_1201, DRB1_1302, DRB1_1501, DRB3_0101, DRB3_0202, DRB4_0101 and DRB5_0101.
21. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the 13 to 16 contiguous amino acid residues of the C1* and C2* are independently selected from 14 to 16 contiguous amino acid residues of the C1* and C2*, 15 to 16 contiguous amino acid residues of the C1* and C2* and 16 contiguous amino acid residues of the C1* and C2*.
22. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the 13 to 16 contiguous amino acid residues of the C3* and C4* are independently selected from 14 to 16 contiguous amino acid residues of the C3* and C4*, 15 to 16 contiguous amino acid residues of the C3* and C4* and 16 contiguous amino acid residues of the C3* and C4*.
23. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the 0-6 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4 are independently selected from 0-5 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4, 0-4 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4, 0-3 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4, 0-2 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4, 0-1 contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4, such as 0 contiguous amino acid residues contiguous amino acid residues of A1, B1, A2, B2, A3, B3, A4 and B4.
24. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the number of amino acid residue substitutions of the C1*, C2*, C3* and C4* are independently selected from 0, 1 or 2.
25. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the number of amino acid residue substitutions of the A1, B1, A2, B2, A3, B3, A4 and B4 are independently selected from 0 or 1.

26. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the total number of amino acid residues in the A1 and B1 of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
- 5 27. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the total number of amino acid residues in A2 and B2 of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
28. The composition according to any one of the preceding claims insofar as they
10 depend on claim 2, wherein the total number of amino acid residues in A3 and B3 of formulas III and III* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
29. The composition according to any one of the preceding claims insofar as they
15 depend on claim 2, wherein the total number of amino acid residues in A4 and B4 of formulas IV and IV* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
30. The composition according to any one of the preceding claims insofar as they
20 depend on claim 2, wherein the total number of amino acid residues in the a, A1, B1 and b of formulas I and I* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
31. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the total number of amino acid residues in the a, A2, B2 and b of formulas II and II' independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
- 25 32. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the total number of amino acid residues in the a, A3, B3 and b of formulas III and III* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.
- 30 33. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the total number of amino acid residues in the a, A4, B4 and b of formulas IV and IV* independently is 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0, or does not exceed 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1.

34. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid residues of a and b independently is 0, 1 or 2 lysine (K).
35. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid residues of a and b independently is 0, 1 or 2 arginine (R).
36. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid residues of a and b independently is 0, 1 or 2 aspartic acid (D).
37. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the amino acid residues of a and b in total is 0, 1, 2 or 3 amino residues.
38. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the length of the peptides each is independently selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25 amino acid residues in length.
39. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein a peptide of formulas I, I*, II, II*, III, III* and/or IV, IV* comprises one or more of the modifications selected from the following:
- g) N-terminal acetylation or methylation
 - h) C terminal amidation
 - i) C-terminal amination
 - j) replacement of one or more hydrogen on the side chain amines of arginine and/or lysine with a methylene group
 - k) glycosylation, and
 - l) phosphorylation.
40. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein any one of the peptides in the composition is a salt .
41. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the peptides of the composition are obtained synthetically or by recombinant expression.

42. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein the peptides are freeze-dried, such as in a freeze-dried state.
43. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein each peptide in the composition is present in a molar
5 concentration of 1 to 1000 μM , preferably 1-100 μM and more preferred in 1-10 μM .
44. The composition according to any one of the preceding claims insofar as they depend on claim 2, wherein each peptide in the composition is present in a soluble form in a molar concentration of 1 to 1000 μM preferably 1-100 μM and more preferred in 1-10 μM .
45. The composition according to any one of the preceding claims insofar as they
10 depend on claim 2, wherein each peptide in the composition is present in equimolar concentrations or in substantially equimolar concentrations.
46. A pharmaceutical composition comprising a composition according to any of claims 1 to 45.
47. The pharmaceutical composition according to claim 46, further comprising a
15 pharmaceutically acceptable carrier, excipient and/or adjuvant, optionally sterile.
48. The pharmaceutical composition according to any one of claims 46 and 47 formulated as a vaccine for parenteral administration.
49. The pharmaceutical composition according to any one of claims 46 and 48, wherein the pharmaceutical composition is a powder.
- 20 50. The pharmaceutical composition according to any one of claims 46 to 49 wherein the composition is formulated to be re-dissolved before use.
51. The pharmaceutical composition according to any one of claims 46 to 50, wherein the composition is isotonic.
52. A kit comprising a compartment and instructions, wherein the compartment
25 comprises a composition according to any one of claims 46 to 51, and wherein the instructions are for use in treating allergy to Japanese cedar pollen (insert Latin name as well in description) or pollen having cross reactivity to Japanese cedar pollen, e.g. pollen from members of the Cupressaceae family (insert specific examples).
53. A method for treating allergy to Japanese cedar pollen, an allergen of Japanese
30 cedar pollen, pollen cross-reactive with Japanese cedar pollen or an allergen cross reacting

with an allergen of Japanese cedar pollen in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a composition according to any of claims 1 to 45, a pharmaceutical composition according to any one of claims 46 to 51 or a kit according to claim 52.

5 54. A method for treating allergy in a subject in need thereof, where signs and/or symptoms of said allergy are elicited by exposure to Japanese cedar pollen, an allergen of Japanese cedar pollen, pollen cross-reactive with Japanese cedar pollen or an allergen cross reacting with an allergen of Japanese cedar pollen, comprising administering to said subject a
10 therapeutically effective amount of a composition according to any of claims 1 to 45, a pharmaceutical composition according to any one of claims 46 to 51 or a kit according to claim 52.

55. The method according to any one of claims 53 and 54, wherein treating the allergy comprises or consists of relieving or reducing an immune response triggered by exposure to said Japanese cedar pollen, said allergen of Japanese cedar pollen, said pollen
15 having cross reactivity to Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

56. The method according to any one of claims 53 and 54, wherein treating the allergy comprises or consists of relieving one or more symptoms of an immune response triggered by exposure to said Japanese cedar pollen, said allergen of Japanese cedar pollen,
20 said pollen having cross reactivity to Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

57. The method according to any one of claims 53 and 54, wherein treating the allergy consists of or comprises inducing immunological tolerance against said Japanese cedar pollen, said allergen of Japanese cedar pollen, said pollen having cross reactivity to
25 Japanese cedar pollen or said allergen cross reacting to said allergen of Japanese cedar pollen.

58. The method according to any one of claims 53 to 57, wherein treating the allergy comprises or consists of relieving one or more symptom(s) associated with allergic rhinitis and/or allergic conjunctivitis and/or allergic asthma and/or allergic eczema (e.g. atopic
30 dermatitis).

59. The method according to any one of claims 53 to 57, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic rhinitis, such as

- reducing the intensity of itchy nose and/or
 - reducing the number of sneezes within a given period (e.g. daily, weekly, monthly) and/or
 - reducing the intensity of blocked nose (congestion) and/or
 - reducing the amount of nasal fluid and/or
 - 5 - reducing the eosinophilic count in nasal fluid and/or
 - reducing specific IgE antibody level (titer) in nasal fluid or in serum and/or
 - reducing basophil histamine release of blood.
60. The method according to any one of claims 53 to 57, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic
- 10 conjunctivitis, such as
- reducing the intensity of itchy eyes, redness in the white of the eyes and/or watery eyes; and/or
 - reducing the eosinophilic count in conjunctival tissue scrapings; and/or
 - reducing specific IgE antibody level (titer) in conjunctival tissue scrapings or in serum;
 - 15 and/or
 - reducing basophil histamine release in blood.
61. The method according to any one of claims 53 to 57, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with allergic
- 20 asthma, such as
- reducing the intensity and/or number of coughs within a given period (e.g. daily, weekly, monthly); and/or
 - reducing the intensity of wheezes; and/or
 - improving being short of breath; and/or
 - improving lung function; and/or
 - 25 - reducing specific IgE antibody level (titer) in lung fluid or in serum; and/or
 - reducing basophil histamine release in blood.
62. The method according to any one of claims 53 to 57, wherein treating the allergy comprises or consists of relieving one or more signs or symptoms associated with atopic
- 30 dermatitis, such as
- reducing itch intensity of the skin; and/or
 - reducing eczema score; and/or
 - reducing number of (peripheral) blood eosinophils.
63. The method according to any one of claims 53 to 62, comprising or consisting of reducing the patient's need for concomitant treatment with corticosteroids or H1

antihistamines to reduce, relieve or suppress one or more symptoms of an immune response associated with the allergy.

64. The method according to any one of claims 53 to 63, wherein the immune response is clinically presented as atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anapylaxis, and/or hay fever.

65. The method according to any one of claims 53 to 64, wherein the method decreases, reduces, suppresses, or inhibits atopic dermatitis, urticaria, contact dermatitis, allergic conjunctivitis, allergic rhinitis, allergic asthma, anaphylaxis, and/or hay fever.

66. The method according to any one of claims 53 to 65, which comprises decreasing a T cell response in the patient against an allergen of Japanese cedar or a cross reacting allergen.

67. The method according to any one of claims 53 to 66, wherein the subject is sensitized to at least one allergen of Japanese cedar, such as to Cry j 1 and/or Cry j 2.

68. The method according to any one of claims 53 to 67, wherein Japanese cedar pollen is pollen of the genus *Cryptomeria*, such as from the species *Cryptomeria japonica*

69. The method according to any one of claims 53 to 68, wherein pollen cross-reactive with Japanese cedar pollen is selected from pollen of the Cupressaceae family, such as from pollen of Japanese cypress (*Chamaecyparis obtuse*), Common cypress (*Cupressus sempervirens*) and Mountain cedar (*Juniperus ashei*).

70. The method according to any one of claims 53 to 69, wherein an allergen of Japanese cedar pollen is Cry j 1 and/or Cry j 2.

71. The method according to any one of claims 53 to 70, wherein an allergen cross reacting with a Japanese cedar pollen allergen is Cha o 1 and/or Cha o 2.

72. A composition according to any of claims 1 to 45, a pharmaceutical composition according to any one of the claims 46 to 51 or a kit according to claim 52 for use in the method according to any one of claims 53 to 71.

73. Use of a composition according to any of claims 1 to 45, a pharmaceutical composition according to any one of the claims 46 to 51 or a kit according to claim 52 for the preparation of a medicament for use in the method according to any one of claims 53 to 71.