CLAIMS

~~1.~~

1. A ~~composition for use in eliciting an immune response in a patient who has a cancer overexpressing an MMP12 polypeptide~~ peptide comprising ~~the~~an amino acid sequence of SEQ ID ~~NO: 26,~~ No. 30 or SEQ ID No. 34 or an amino acid sequence selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110, and variant sequences thereof which are at least 88% homologous to SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110, and wherein said variant binds to molecule(s) of the major histocompatibility complex (MHC) and/or induces T cells cross-reacting with said variant peptide, wherein said peptide is not a full-length polypeptide.

2. The peptide according to claim 1, wherein said peptide has the ability to bind to an MHC class-I or –II molecule, and wherein said peptide, when bound to said MHC, is capable of being recognized by CD4 and/or CD8 T cells.

3. The peptide or variant thereof according to claim 1 or 2, wherein the amino acid sequence thereof comprises a continuous stretch of amino acids according to any one of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110.

4. The peptide or variant thereof according to any of claims 1 to 3, wherein said peptide or variant thereof has an overall length of from 8 to 100, preferably from 8 to 30, and more preferred from 8 to 16 amino acids, and most preferred wherein the peptide consists or consists essentially of an amino acid sequence according to any of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110.

5. The peptide or variant thereof according to any of Claims 1 to 4, wherein said peptide is modified and/or includes non-peptide bonds.

6. The peptide or variant thereof according to any of Claims 1 to 5, wherein said peptide is part of a fusion protein, in particular comprising ~~a population of~~N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii).

7. A nucleic acid, encoding for a peptide or variant thereof according to any one of claims 1 to 6, optionally linked to a heterologous promoter sequence.

8. An expression vector expressing the nucleic acid according to claim 7.

9. A recombinant host cell comprising the peptide according to claim 1 to 6, the nucleic acid according to claim 7 or the expression vector according to claim 8, wherein said host cell preferably is an antigen presenting cell such as a dendritic cell.

10. The peptide or variant thereof according to any one of claims 1 to 6, the nucleic acid according to claim 7, the expression vector according to claim 8, or the host cell according to claim 9 for use in medicine.

11. A method for producing the peptide or variant thereof according to any one of claims 1 to 6, the method comprising culturing the host cell according to claim 9 that presents the peptide according to claim 1 to 6, or expresses the nucleic acid according to claim 7 or bears the expression vector according to claim 8, and isolating the peptide or variant thereof from the host cell or its culture medium.

12. An *in vitro* method for producing activated T ~~cells that kill cancer cells, wherein the activated T cells are cytotoxic CD8+ T cells produced by~~ lymphocytes, the method comprising contacting *in vitro* T cells with ~~an antigen presenting cell that presents a peptide consisting of the amino acid sequence of SEQ ID NO: 26 in a complex with an MHC class I molecule~~antigen loaded human class I or II MHC molecules expressed on the surface of ~~the~~a suitable antigen~~-~~presenting cell ~~in vitro,~~or an artificial construct mimicking an antigen-presenting cell for a period of time sufficient to activate said T ~~cell, and wherein said~~ cells in an antigen specific manner, wherein said antigen is a peptide according to any one of claims 1 to 4.

13. An activated T lymphocyte, produced by the method according to claim 12, that selectively recognizes a cell which presents a polypeptide comprising an amino acid sequence given in any one of claims 1 to 4.

14. A method for killing target cells in a patient which target cells present a polypeptide comprising an amino acid sequence given in any one of claims 1 to 4, the method comprising administering to the patient an effective number of activated T cells as defined in claim 13.

15. An antibody, in particular a soluble or membrane-bound antibody, that specifically recognizes the peptide or variant thereof according to any of claims 1 to 5, preferably the peptide or variant thereof according to any of claims 1 to 5 when bound to an MHC molecule..

16. Use of a peptide according to any one of claims 1 to 6, the nucleic acid according to claim 7, the expression vector according to claim 8, the cell according to claim 9, the activated T lymphocyte according to claim 13 or the antibody according to claim 15 for the treatment of cancer or in the manufacture of a medicament against cancer.

~~1.~~17. The use according to claim 16, wherein said cancer is selected from the group ~~consisting of lung cancer, stomach cancer, and liver cancer~~of lung cancer, brain cancer, breast cancer, colorectal cancer, esophageal cancer, kidney cancer, liver cancer, ovarian cancer, pancreatic cancer, prostate cancer, gastric cancer, melanoma, merkel cell carcinoma, leukemia (AML, CLL) and other tumors that show an overexpression of a protein from which a peptide SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110 is derived from.

18. ~~2. Use of a~~ A kit comprising:

(a) a container comprising a pharmaceutical composition containing the peptide(s) or the variant according to any one of claims 1 to 6, the nucleic acid(s) according to claim 7, the expression vector(s) according to claim 8, the cell(s) according to claim 10, the activated T lymphocyte(s) according to claim 13 or the antibody according to claim 15, in solution or in lyophilized form;

(b) optionally, a second container containing a diluent or reconstituting solution for the lyophilized formulation;
(c) optionally, at least one more peptide selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 162, and
(d) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

19. The kit according to claim 18, further comprising one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle, (v) a syringe, or (viii) an adjuvant.

20. The kit according to claim 18 or 19, wherein said peptide is selected from the group consisting of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110.

21. A method for producing a personalized anti-cancer vaccine, said method comprising:
a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from said individual patient;
b) comparing the peptides as identified in a) with a warehouse of peptides that have been pre-screened for immunogenicity and/or over-presentation in tumors as compared to normal tissues
c) selecting at least one peptide from the warehouse that matches a TUMAP identified in the patient; and
d) formulating the personalized vaccine based on step c).

22. The method according to claim 21, wherein said TUMAPs are identified by:
a1) comparing expression data from the tumor sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumor sample to identify proteins that are over-expressed or aberrantly expressed in the tumor sample; and
a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumor sample to identify MHC ligands derived from proteins over-expressed or aberrantly expressed by the tumor.

23. The method according to claim 21 or 22, wherein the sequences of MHC ligands are identified by eluting bound peptides from MHC molecules isolated from the tumor sample, and sequencing the eluted ligands.

24. The method according to any of claims 21 to 23, wherein the normal tissue corresponding to the tissue type of the tumor sample is obtained from the same patient.

25. The method according to any of claims 21 to 24, wherein the peptides included in the warehouse are identified based on the following steps:
aa. Performing genome-wide messenger ribonucleic acid (mRNA) expression analysis by highly parallel methods, such as microarrays or sequencing-based expression profiling, comprising identify genes that over-expressed in a malignant tissue, compared with a normal tissue or tissues;
ab. Selecting peptides encoded by selectively expressed or over-expressed genes as detected in step aa, and
ac. Determining an induction of in vivo T-cell responses by the peptides as selected comprising *in vitro* immunogenicity assays using human T cells from healthy donors or said patient; or
ba. Identifying HLA ligands from said tumor sample using mass spectrometry;
bb. Performing genome-wide messenger ribonucleic acid (mRNA) expression analysis by highly parallel methods, such as microarrays or sequencing-based expression profiling, comprising identify genes that over-expressed in a malignant tissue, compared with a normal tissue or tissues;
bc. Comparing the identified HLA ligands to said gene expression data;
bd. Selecting peptides encoded by selectively expressed or over-expressed genes as detected in step bc;
be. Re-detecting of selected TUMAPs from step bd on tumor tissue and lack of or infrequent detection on healthy tissues and confirming the relevance of over-expression at the mRNA level; and
bf. Determining an induction of in vivo T-cell responses by the peptides as selected comprising *in vitro* immunogenicity assays using human T cells from healthy donors or said patient.

26. The method according to any of claims 21 to 25, wherein the immunogenicity of the peptides included in the warehouse is determined by a method comprising in vitro immunogenicity assays, patient immunomonitoring for individual HLA binding, MHC multimer staining, ELISPOT assays and/or intracellular cytokine staining.

27. The method according to any of claims 21 to 26, wherein said warehouse comprises a plurality of peptides selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 162.

28. The method according to any of claims 21 to 27, further comprising identifying at least one mutation that is unique to the tumor sample relative to normal corresponding tissue from the individual patient, and selecting a peptide that correlates with the mutation for inclusion in the vaccine or for the generation of cellular therapies.

29. The method according to claim 28, wherein said at least one mutation is identified by whole genome sequencing.

30. A T-cell receptor, preferably soluble or membrane-bound, that is reactive with an HLA ligand, wherein said ligand has at least 75% identity to an amino acid sequence selected from the group consisting of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110.

31. The T-cell receptor according to claim 30, wherein said amino acid sequence is at least 88% identical to SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110.

32. The T-cell receptor according to claim 30 or 31, wherein said amino acid sequence consists any of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110 .

33. The T-cell receptor according to any of claims 30 to 32, wherein said T-cell receptor is provided as a soluble molecule and optionally carries a further effector function such as an immune stimulating domain or toxin.

34. A nucleic acid, encoding for a TCR according to any one of claims 30 to 33, optionally linked to a heterologous promoter sequence.

35. An expression vector capable of expressing the nucleic acid according to claim 34.

36. A host cell, comprising the nucleic acid according to claim 34 or the nucleic acid encoding an antibody according to claim 15 or the expression vector according to claim 35, wherein said host cell preferably is a T cell or NK cell.

37. A method for producing the T cell receptor according to any claims 30 to 33, said method comprising culturing a host cell according to Claim 36, and isolating said T cell receptor from said host cell and/or its culture medium.

38. A pharmaceutical composition ~~in the manufacture of a medicament for eliciting an immune response in a patient who has a cancer overexpressing an MMP12 polypeptide~~ comprising at least one active ingredient selected from the group consisting of

a) a peptide selected from the ~~amino acid sequence~~group consisting of SEQ ID ~~NO: 26, said composition~~No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110;

b) a T-cell receptor reactive with a peptide and/or the peptide-MHC complex according to a);

c) a fusion protein comprising a ~~population~~peptide according to a), and the N-terminal amino acids 1 to 80 of the HLA-DR antigen-associated invariant chain (Ii);

d) a nucleic acid encoding for any of a) to c) or an expression vector comprising said nucleic acid,

e) a host cell comprising the expression vector of d,

~~a)~~f) an activated T ~~cells that kill cancer cells, wherein the activated T cells are cytotoxic CD8+ T cells produced~~-lymphocyte, obtained by a method comprising contacting in vitro T cells with ~~an antigen presenting cell that presents a peptide consisting of the amino acid~~

~~sequence of SEQ ID NO: 26 in a complex with an MHC class I molecule~~a peptide according to a) expressed on the surface of ~~the~~a suitable antigen presenting cell ~~in vitro,~~ for a period of time sufficient to activate said T cell~~, and wherein said cancer is selected from the group consisting of lung cancer, stomach cancer, and liver cancer.~~ in an antigen specific manner, as well as a method to transfer these activated T cells into the autologous or other patients;

g) ~~3.~~ an antibody, or soluble T-cell receptor, reactive to a peptide and/or the peptide – MHC complex according to a) and/or a cell presenting a peptide according to a), and potentially modified by fusion with for example immune-activating domains or toxins,

h) an aptamer recognizing a peptide selected from the group consisting of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 110 and/or a complex of a peptide selected from the group consisting of SEQ ID No. 33, SEQ ID No. 34, SEQ ID No, 1 to SEQ ID No. 29, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, and SEQ ID No. 35 to SEQ ID No. 162 with a MHC molecule,

i) a conjugated or labelled peptide or scaffold according to any of a) to h) and a pharmaceutically acceptable carrier, and optionally, pharmaceutically acceptable excipients and/or stabilizers.

The pharmaceutical composition ~~of~~according to claim ~~1 or use of claim 2~~38, wherein ~~the T cells are autologous to the patient.~~

~~2.~~39. ~~4. The~~ (i) the pharmaceutical composition ~~of claim 1 or use of claim 2,~~further comprises an adjuvant, and/or (ii) wherein the ~~T cells are obtained from a healthy donor~~pharmaceutical composition is a vaccine or a cellular therapeutic agent.

~~5.~~ The pharmaceutical composition ~~of claim 1 or use of claim 2, wherein the T cells are obtained from tumor infiltrating lymphocytes or peripheral blood mononuclear cells.~~

~~6. The composition of claim 1 or use of claim 2, wherein the activated T cells are expanded in vitro.~~

~~7. The composition of claim 1 or use of claim 2, wherein the antigen presenting cell is infected with a recombinant virus expressing the peptide.~~

~~8. The composition or use of claim 7, wherein the antigen presenting cell is a dendritic cell or a macrophage.~~

~~9. The composition or use of claim 6, wherein the expansion is in the presence of an anti-CD28 antibody and IL-12.~~

~~10. The composition of claim 1 or use of claim 2, wherein the population of activated T cells are administered in the form of a composition.~~

~~11. The composition or use of claim 10, wherein the composition further comprises an adjuvant.~~

~~12. The composition or use of claim 11, wherein the adjuvant is selected from the group consisting of anti-CD40 antibody, imiquimod, resiguimod, GM-CSF, cyclophosphamide, Sunitinib, bevacizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly (1:C) and derivatives, RNA, sildenafil, and particulate formations with poly(lactide coglycolide) (PLG), virosomes, interleukin (IL) 1, IL-2, IL-4, IL-7, IL-12, IL-13, IL-15, IL-21, and IL-23.~~

~~13. The composition of claim 1 or use of claim 2, wherein the cancer is lung cancer.~~

~~14. The composition of claim 1 or use of claim 2, wherein the cancer is stomach cancer.~~

~~15. The composition of claim 1 or use of claim 2, wherein the cancer is liver cancer.~~

~~16. The composition of claim 1 or use of claim 2, wherein the MHC molecule is HLA-A*24.~~

3.40. ~~17. The composition or use of claim 11~~according to claim 39, wherein the adjuvant ~~comprises IL-2~~is an interleukin, including IL-2, IL-15 or a combination thereof.

~~18. The composition or use of claim 11, wherein the adjuvant comprises IL-7.~~

~~19. The composition or use of claim 11, wherein the adjuvant comprises IL-12.~~

~~20. The composition or use of claim 11, wherein the adjuvant comprises IL-15.~~

4.41. ~~21. The composition or use of claim 11, wherein the adjuvant comprises IL-21.~~An aptamer that specifically recognizes the peptide or variant thereof according to any of

claims 1 to 4, preferably the peptide or variant thereof according to any of claims 1 to 4 that is bound to an MHC molecule.