CLAIMS

1. A peptide comprising an amino acid sequence of SEQ ID No. 222 or an amino acid sequence selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388, and variant sequences thereof that are at least 88% homologous to SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388, 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; and a pharmaceutical acceptable salt thereof, 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. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388.

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. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388.

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 N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii).

7. A nucleic acid, encoding 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 capable of expressing the nucleic acid according to claim 7.

9. A recombinant host cell comprising the peptide according to any one of 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 expresses 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 lymphocytes, the method comprising contacting in vitro T cells with antigen loaded human class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell or an artificial construct mimicking an antigen-presenting cell for a period of time sufficient to activate said T 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 use in diagnosis and/or treatment of cancer, or for use in the manufacture of a medicament against cancer.

17.

~~1. A composition for use in the treatment of a patient who has cancer comprising a population of activated T cells that selectively recognize cancer cells that present a peptide consisting of the amino acid sequence of SYVKVLHHL (SEQ ID NO: 241),~~
~~wherein the peptide is in a complex with an MHC molecule,~~

The use according to claim 16, wherein said cancer is selected from the group ~~consisting~~ of glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell ~~lung cancer,~~ and small cell lung cancer, Non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer including cancer of the gastric ~~-~~-esophageal junction, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, ~~head-and neck squamous cell carcinoma, and uterine cancer.~~or uterine cancer, and other tumours that show an overexpression of a protein from which a peptide SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388 is derived from.

~~2. Use of~~ 18. 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 ~~the manufacture of a medicament~~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. 417, 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, (vii) a syringe, or (viii) an adjuvant.

20. ~~treatment of a~~The kit according to claim 18 or 19, wherein said peptide is selected from the group consisting of SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388.

21. A method for producing a personalized anti-cancer vaccine or a compound-based and/or cellular therapy for an individual patient, said method comprising:

a) identifying tumour-associated peptides (TUMAPs) presented by a tumour 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 tumours 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 or compound-based or cellular therapy based on step c).

22. The method according to claim 21 , wherein said TUMAPs are identified by:

a1) comparing expression data from the tumour sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumour sample to identify proteins that are over-expressed or aberrantly expressed in the tumour sample; and

a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumour sample to identify MHC ligands derived from proteins over-expressed or aberrantly expressed by the tumour.

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 tumour 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 tumour sample is obtained from the same patient.

25. The method according to any one 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 tumour 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;

be. 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 be;

be. Re-detecting of selected TUMAPs from step bd on tumour 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. 417.

28. ~~whe~~The method according to any of claims 21 to 27, further comprising identifying at least one mutation that is unique to the tumour 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 ~~cancer, said~~ at least 75% identity to an amino acid sequence selected from the group consisting of SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388.

31. The T-cell receptor according to claim 30, wherein said amino acid sequence is at least 88% identical to SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388.

32. The T-cell receptor according to claim 30 or 31 , wherein said amino acid sequence consists any of SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388 .

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 comprising ~~a population of activated T cells that selectively recognize cancer cells that present a peptide consisting of the amino acid sequence of SYVKVLHHL (SEQ ID NO: 241), wherein the peptide is in a~~ at least one active ingredient selected from the group consisting of

a) the peptide selected from the group consisting of SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388;

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

~~wherein said cancer is selected from the group consisting of glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell lung cancer, and small cell lung cancer, Non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer including cancer of the gastric esophageal junction, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head-and neck squamous cell carcinoma, and uterine cancer.~~

~~3. The composition of claim 1 or use of claim 2, wherein the T cells are autologous to the patient.~~

~~4. The composition of claim 1 or use of claim 2, wherein the T cells are obtained from a healthy donor.~~

~~5. The composition of claim 1 or use of claim 2, wherein the~~ c) a fusion protein comprising a 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,

f) an activated T~~ cells are produced by~~ -lymphocyte, obtained by a method comprising contacting in vitro T cells with ~~the~~a peptide ~~loaded human class I or II MHC molecules~~according to a) expressed on the surface of ~~an~~a suitable antigen-presenting cell for a period of time sufficient to activate ~~the T cells.~~said T cell in an antigen specific manner, as well as a method to transfer these activated T cells into the autologous or other patients;

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

~~7. The composition of claim 1 or use of claim 2, wherein the~~ -cell receptor, reactive to a peptide ~~is in a~~ and/or the peptide - MHC complex ~~with the class I MHC molecule.~~

~~8. The composition~~ according to a) and/or ~~use of claim 5, wherein the antigen~~ a cell presenting ~~cell is infected with a recombinant virus expressing the peptide.~~

~~9. The composition~~a peptide according to a), and potentially modified by fusion with for example immune- activating domains or ~~use of claim 8, wherein the antigen presenting cell is a dendritic cell or a macrophage.~~toxins,

h) an aptamer recognizing a peptide ~~10. The composition or use of claim 6, wherein the expansion is in the presence of an anti-CD28 antibody and IL-12.~~

~~11. The composition of claim 1 or use of claim 2, wherein the population of activated T cells comprises CD8-positive cells.~~

~~12. The composition or use of claim 5, wherein the contacting is *in vitro*.~~

~~13. The composition of claim 1 or use of claim 2, wherein the population of activated T cells are to be administered in the form of a composition.~~

~~14. The composition or use of claim 13, wherein the composition comprises an adjuvant.~~

~~15. The composition or use of claim 14, wherein the adjuvant is~~ selected from the group consisting of ~~anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, Sunitinib, bevacizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly-(I:C) and derivatives, RNA, sildenafil, particulate formulations 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.~~

~~16. The composition of claim 1 or use of claim 2, wherein the cancer is hepatocellular carcinoma.~~

~~17. A composition for use in eliciting an immune response in a patient who has cancer comprising a population of activated T cells that selectively recognize cancer cells that present a peptide consisting of the amino acid sequence of SYVKVLHHL (~~SEQ ID ~~NO: 241),~~ ~~wherein the peptide is in a~~ No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and SEQ ID No. 324 to SEQ ID No. 388 and/or a complex ~~with an MHC molecule,~~

> ~~wherein said cancer is~~ of a peptide selected from the group consisting of ~~glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell lung cancer, and small cell lung cancer, Non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer including cancer of the gastric esophageal junction, gallbladder cancer~~SEQ ID No. 222, SEQ ID No. 1 to SEQ ID No. 155, SEQ ID No. 157 to SEQ ID No. 221, SEQ ID No. 223 to SEQ ID No. 322 and ~~cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head and neck squamous cell carcinoma, and uterine cancer.~~SEQ ID No. 324 to SEQ ID No. 388 with a MHC molecule,

~~18. Use of a composition in the manufacture of a medicament for eliciting an immune response in a patient who has cancer comprising, said composition comprising a population of activated T cells that selectively recognize cancer cells that present a peptide consisting of the amino acid sequence of SYVKVLHHL (SEQ ID NO: 241), wherein the peptide is in a complex with an MHC molecule,~~

~~wherein said cancer is selected from the group consisting of glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell lung cancer, and small cell lung cancer, Non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer including cancer of the gastric esophageal junction, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head and neck squamous cell carcinoma, and uterine cancer.~~

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.

39. The pharmaceutical composition according to claim 38, wherein (i) the pharmaceutical composition further comprises an adjuvant, and/or (ii) wherein the pharmaceutical composition is a vaccine or a cellular therapeutic agent.

40. The pharmaceutical composition according to claim 39~~19. The composition of claim 17 or use of claim 18, wherein the activated T cells are produced by contacting T cells with the peptide loaded human class I or 11 MHC molecules expressed on the surface of an antigen-presenting cell for a period of time sufficient to activate the T cells.~~

~~20. The composition of claim 17 or use of claim 18, wherein the immune response comprises a cytotoxic T cell response.~~

~~21. The composition of claim 17 or use of claim 18, wherein the immune response is capable of killing the cancer cells.~~

~~22. The composition of claim 17 or use of claim 18, wherein the cancer is hepatocellular carcinoma.~~

~~23. The composition or use of claim 14, wherein the adjuvant comprises IL-7.~~

~~24. The composition or use of claim 14~~, wherein the adjuvant ~~comprises~~ is an interleukin, including IL-2, IL-15 or a combination thereof.

41. An aptamer 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 that is bound to an MHC molecule.

~~25. The composition of claim 1 or use of claim 2, wherein the cancer is breast cancer.~~

~~26. The composition of claim 1 or use of claim 2, wherein the cancer is non-small cell lung cancer.~~

~~27. The composition of claim 1 or use of claim 2, wherein the cancer is small cell lung cancer.~~

~~28. The composition of claim 1 or use of claim 2, wherein the peptide is in a complex with HLA-A*24.~~