~~Claims~~
CLAIMS

1. A peptide consisting of ~~the~~an amino acid sequence of ~~GVYDGEEHSV (~~SEQ ID No. 303~~), wherein the peptide is in the form of~~ ; or a pharmaceutically acceptable salt thereof.

~~2. A pharmaceutical composition comprising a peptide selected from the group of a peptide consisting of the sequence according to SEQ ID No. 303,~~
~~the~~

2. The peptide or salt thereof according to claim 1, wherein said peptide has the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I, and wherein said peptide, when bound to MHC, is capable of being recognized by CD8 T cells.

3. The peptide or salt thereof according to ~~a), whereby~~any of Claims 1 to 2, wherein said peptide includes non-peptide bonds~~; and~~.

~~the~~

4. The peptide or salt thereof according to ~~a), whereby~~any of Claims 1 to 3, wherein said peptide is ~~a~~ part of a fusion protein, in particular comprising ~~the~~ N-terminal amino acids of the HLA-DR antigen--associated invariant chain (Ii~~), or fused to (or into the sequence of) an antibody,~~).

5. A nucleic acid, encoding a peptide according to any one of claims 1 to 4, optionally linked to a heterologous promoter sequence.

6. An expression vector capable of expressing the nucleic acid according to claim 5.

7. The peptide or salt thereof according to any one of claims 1 to 4, the nucleic acid according to claim 5 or the expression vector according to claim 6 for use in medicine.

8. A host cell comprising the peptide according to claim 1 to 4, the nucleic acid according to claim 5 or the expression vector according to claim 6, wherein said host cell optionally is an antigen presenting cell such as a dendritic cell.

9. A method for producing the peptide according to any one of claims 1 to 4, the method comprising culturing the host cell according to claim 8 that presents the peptide according to claim 1 to 4, or expresses the nucleic acid according to claim 5 or the expression vector according to claim 6, and isolating the peptide from the host cell or its culture medium.

10. ~~together with at least one suitable carrier and/or excipient for use in the treatment of Hepatocellular carcinoma cancer (HCC).~~

~~3. A pharmaceutical composition comprising an activated cyctototoxic T lymphocyte (CTL), produced by an~~ An *in vitro* method for producing activated T lymphocytes, the method comprising contacting *in vitro* ~~CTL~~T cells with antigen loaded human class I ~~Major Histocompatibility Complex (MHC)~~ 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.

11. An activated T cell, produced by the method according to claim 10, that selectively recognizes a cell which presents a polypeptide comprising an amino acid sequence given in any one of claims 1 to 3.

12. Use of an effective number of activated T cells as defined in claim 11 in the manufacture of a medicament for killing target cancer cells in an individual which target cancer cells present a polypeptide according to any one of claims 1 to 4.

13. An antibody, soluble or membrane-bound, that specifically recognizes the peptide according to any of claims 1 to 3, optionally the peptide according to any of claims 1 to 3 that is bound to an MHC molecule.

14. The peptide or salt thereof according to any one of claims 1 to 4, the nucleic acid according to claim 5, the expression vector according to claim 6, the cell according to claim 8, the activated T lymphocyte according to claim 11 or the antibody according to claim 13 for use in the diagnosis and/or the treatment of cancer.

15. The peptide, the nucleic acid, the expression vector, the cell, the activated T lymphocyte or the antibody for use according to claim 14, wherein said cancer is selected from the group of HCC, brain cancer, kidney cancer, pancreatic cancer, colon or rectal cancer or leukemia and other tumors that show an overpresentation of a peptide of SEQ ID No. 303.

16. A kit comprising:

(a) a container comprising a pharmaceutical composition containing the peptide(s) or the salt according to any one of claims 1 to 4, the nucleic acid(s) according to claim 5, the expression vector(s) according to claim 6, the cell(s) according to claim 8, the activated T lymphocyte(s) according to claim 11 or the antibody according to claim 13, 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. 346, and

(d) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

17. The kit according to claim 16, 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.

18. A method for producing a personalized anti-cancer vaccine for a compound-based and/or cellular therapeutic agent for an individual, said method comprising:

a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from the individual;

b) comparing the peptides as identified in a) with a warehouse of peptides that have been prescreened 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 tumor-associated peptide identified in the individual; and

d) manufacturing the personalized vaccine or compound-based or cellular therapeutic agent product based on step c),
wherein said warehouse comprises a peptide consisting of the sequence of SEQ ID No. 303.

19. The method according to claim 18, 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.

20. The method according to claim 18 or 19, 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.

21. The method according to any of claims 18 to 20, wherein the normal tissue corresponding to the tissue type of the tumor sample is obtained from the same individual.

22. The method according to any of claims 18 to 21, 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 individual; 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 individual.

23. The method according to any of claims 18 to 22, 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.

24. The method according to any of claims 18 to 23, further comprising identifying at least one mutation that is unique to the tumor sample relative to normal corresponding tissue from the individual, and selecting a peptide that correlates with the mutation for inclusion in the vaccine or for the generation of cellular therapeutic agents.

25. The method according to claim 24, wherein said at least one mutation is identified by whole genome sequencing.

26. A T-cell receptor, soluble or membrane-bound, that is reactive with an HLA ligand, wherein said ligand is is the peptide or salt thereof according to any of claims 1 to 4, optionally the peptide or salt thereof according to any of claims 1 to 4 when bound to an MHC molecule.

27. The T-cell receptor according to claim 26, 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.

28. A nucleic acid, encoding for a TCR according to any one of claims 26 to 27, optionally linked to a heterologous promoter sequence.

29. An expression vector capable of expressing the nucleic acid according to claim 28.

30. A host cell comprising the nucleic acid according to claim 28 or the nucleic acid encoding an antibody according to claim 13 or the expression vector according to claim 29, wherein said host cell optionally is a T cell or NK cell.

31. A method for producing the T cell receptor according to any claims 26 to 27, 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.

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32. A pharmaceutical composition comprising at least one active ingredient selected from the group consisting of

a) a peptide consisting of SEQ ID No. 303, or a pharmaceutically acceptable salt thereof ;

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

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-lymphocyte, obtained by a method comprising contacting in vitro T cells with a peptide according to a) expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate ~~CTL in an antigen specific manner, wherein said antigen is a peptide consisting of SEQ ID No. 303, that selectively recognizes a cell which aberrantly expresses a polypeptide comprising an amino acid sequence consisting~~

~~of SEQ ID No. 303, together with at least one suitable carrier and/or excipient.~~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;

~~4. An antibody that is specific against the MHC/peptide complex of MHC with a peptide consisting of SEQ ID No. 303 for use in immunotoxin therapy in HCC.~~

g)

~~5. Use of~~ an antibody ~~that is specific against the MHC/peptide complex of MHC with a peptide consisting of SEQ ID No. 303 in the manufacture of a medicament for the treatment via immunotoxin therapy in HCC~~, or soluble ~~.~~

~~6. An antibody that is specific against the MHC/peptide complex of MHC with a peptide consisting of SEQ ID No. 303 in ELISA, immunohistochemistry, and/or *in vivo* imaging in HCC.~~

~~7. A~~ T-cell receptor ~~(TCR), soluble or membrane-bound, that is,~~ reactive ~~with an HLA ligand wherein said ligand consists of the amino acid sequence of SEQ ID No. 303.~~

~~8. The T-cell receptor according~~ to ~~claim 7, wherein the ligand is part of~~ a peptide- and/or the peptide - MHC complex~~.~~

~~9. A peptide consisting of the sequence~~ according to ~~SEQ ID No. 303 for use in the treatment~~a) and/or ~~diagnosis of HCC~~a cell ~~.~~

~~10. Use of a peptide consisting of the sequence according to SEQ ID No. 303 in the manufacture of a medicament for the treatment and/or diagnosis of HCC.~~

~~11. An activated CTL produced by an *in vitro* method comprising contacting *in vitro* CTL with antigen loaded human class I MHC molecules expressed on the surface of a suitable antigen-~~ presenting ~~cell for a period of time sufficient to activate CTL in an antigen specific manner, wherein said antigen is a peptide consisting of SEQ ID No. 303, for use in the treatment and/or diagnosis of HCC~~a peptide according to a), and potentially modified by fusion with for example~~.~~

~~12.-Use of an activated CTL produced by an *in vitro* method comprising contacting *in vitro* CTL with antigen loaded human class I MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate CTL in an antigen specific manner, wherein said antigen is a peptide consisting of SEQ ID No. 303, in the manufacture of a medicament for the treatment and/or diagnosis of HCC.~~

~~13.-A composition comprising a population of activated T cells able to selectively recognize HCC in a patient, wherein the cancer cells aberrantly express a peptide consisting of the amino acid sequence of GVYDGEEHSV (SEQ ID NO: 303), and the peptide is in a complex with an MHC molecule, for use in eliciting an~~ immune ~~response in the patient with hepatocellular carcinoma ,wherein the medicament is to be administered to the patient.~~-activating domains or toxins,

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

33. The pharmaceutical composition according to claim 32, wherein (i) the pharmaceutical

~~14.-Use of a composition comprising a population of activated T cells able to selectively recognize HCC in a patient, wherein the cancer cells aberrantly express a peptide consisting of the amino acid sequence of GVYDGEEHSV (SEQ ID NO: 303), and the peptide is in a complex with an MHC molecule, in the manufacture of a medicament for eliciting an immune response in the patient with hepatocellular carcinoma, wherein the medicament is to be administered to the patient.~~

~~15.-The use of claim 14, wherein the T cells are autologous to the patient.~~

~~16.-The use of claim 14, wherein the T cells are obtained from a healthy donor.~~

~~17.-The use of claim 14, wherein the T cells are obtained from tumor infiltrating lymphocytes or peripheral blood mononuclear cells.~~

~~18.- The use of claim 14, wherein the activated T cells are expanded *in vitro*.~~

~~19.-The use of claim 14, wherein the MHC molecule is a class I molecule.~~

~~20. The use of claim 14, wherein the~~ composition further comprises an adjuvant, and/or (ii) wherein the pharmaceutical composition is a vaccine or a cellular therapeutic agent.

34. The pharmaceutical composition according to claim 33, wherein the adjuvant is an interleukin, including IL-2, IL-15 or a combination thereof.~~21. The use of claim 20, wherein the adjuvant is selected from the group consisting of imiquimod, resiguimod, GM-CSF, cyclophosphamide, Sunitinib, bevacizumab, interferon-alpha, CpG oligonucleotides and derivatives, poly (I:C) and derivatives, RNA, sildenafil, and particulate formations with poly(lactid co-glycolid) (PLG) and virosomes.~~

~~22. The use of claim 14, wherein the activated T cells are cytotoxic T cells produced by contacting T cells with an antigen presenting cell that expresses the peptide in a complex with an MHC class I molecule on the surface of the antigen presenting cell, for a period of time sufficient to activate said T cell specifically against the peptide.~~

~~23. The use of claim 22, wherein the T cells contact with an antigen presenting cell *in vitro*.~~

~~24. The use of claim 22, wherein the antigen presenting cell is infected with a recombinant virus expressing the peptide.~~

~~25. The use of claim 24, wherein the antigen presenting cell is a dendritic cell or a macrophage.~~

~~26. The use of claim 18, wherein the activated T cells are expanded in the presence of an anti-CD28 antibody and IL-12.~~

~~27. The use of claim 14, wherein the population of activated T cells comprises CD8-positive cells.~~

~~28. A composition comprising a peptide consisting of the amino acid sequence of GVYDGEEHSV (SEQ ID NO: 303) for use in eliciting an immune response in a patient who has HCC, wherein the composition is to be administered to the patient to induce a T cell response.~~

~~29. Use of a composition comprising a peptide consisting of the amino acid sequence of GVYDGEEHSV (SEQ ID NO: 303) in the manufacture of a medicament to elicit an immune response in a patient who has HCC, wherein the medicament is to be administered to the patient to induce a T cell response.~~

~~30. The use of claim 29, wherein the T cell response is a cytotoxic T cell response.~~

~~31. The use of claim 29, wherein the peptide is in the form of a pharmaceutically acceptable salt.~~