

Claims

1. ~~A pharmaceutically acceptable salt of peptide, wherein the peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 290, SEQ ID NO: 1 to SEQ ID NO: 251, SEQ ID NO: 289 and SEQ ID NO: 291, a sequence length variant of said peptide comprising 1 to 4 additional amino acids at the C- and/or N-terminus thereof, and a variant sequence of said peptide that is modified by at least one conservative amino acid substitution, 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; and wherein said peptide or variant thereof has a maximum length of 16 amino acids.~~
2. ~~The pharmaceutically acceptable salt of claim 1, wherein the pharmaceutically acceptable salt is selected from chloride or acetate salts, optionally wherein the acetate salt is a trifluoroacetate salt.~~
3. ~~Use of a peptide consisting of SEQ ID No. 290 in the manufacture of a medicament against prostate cancer.~~
2. ~~The peptide according to claim 1, wherein said peptide or variant thereof 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 any of claims 1 to 2, wherein said peptide or variant thereof has an overall length of 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: 290, SEQ ID NO: 1 to SEQ ID NO: 251, SEQ ID NO: 289 and SEQ ID NO: 291.~~
4. ~~The peptide or variant thereof according to any of Claims 1 to 3, wherein said peptide is modified and/or includes non-peptide bonds.~~

5. ~~The peptide or variant thereof according to any of Claims 1 to 4, 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).~~
- 6.4. ~~Use of an antibody, in particular a soluble or membrane-bound antibody, preferably optionally a monoclonal antibody or fragment thereof, that specifically recognizes the a peptide or variant thereof according to any of claims 1 to 4 consisting of SEQ ID No. 290, preferably or the peptide or variant thereof according to any of claims 1 to 4 consisting of SEQ ID No. 290 when bound to an MHC molecule, in the manufacture of a medicament against prostate cancer.~~
- 7.5. ~~AUse of a T-cell receptor, preferably soluble or membrane-bound, or a fragment thereof, that is reactive with an HLA ligand, wherein said ligand is the a peptide or variant thereof according to any of claims 1 to 4 consisting of SEQ ID No. 290, preferably or the peptide or variant thereof according to any of claims 1 to 4 consisting of SEQ ID No. 290 when bound to an MHC molecule, in the manufacture of a medicament against prostate cancer.~~
8. ~~The T-cell receptor according to claim 7, wherein said ligand amino acid sequence is at least 88% identical to any one of SEQ ID NO: 290, SEQ ID NO: 1 to SEQ ID NO: 251, SEQ ID NO: 289 and SEQ ID NO: 291, or wherein said ligand amino acid sequence consists of any one of SEQ ID NO: 290, SEQ ID NO: 1 to SEQ ID NO: 251, SEQ ID NO: 289 and SEQ ID NO: 291.~~
- 9.6. ~~The use T-cell receptor according to claim 7 or 85, 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.~~
10. ~~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.~~

~~11.7. Use of aA nucleic acid, or an expression vector expressing said nucleic acid, wherein the nucleic acid encodes for a peptide or variant thereof according to any one of claims 1 to 4 consisting of SEQ ID No. 290, an antibody or fragment thereof according to claim 6 that specifically recognizes a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ ID No. 290 when bound to an MHC molecule, or a T-cell receptor or fragment thereof according to claim 7 or 8 that is reactive with an HLA ligand, wherein said ligand is a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ ID No. 290 when bound to an MHC molecule, optionally linked to a heterologous promoter sequence, or an expression vector expressing said nucleic acid,~~
in the manufacture of a medicament against prostate cancer.

~~12.8. Use of Aa recombinant host cell comprising the peptide according to any one of claims 1 to 6 consisting of SEQ ID No. 290, the an antibody or fragment thereof according to claim 6 that specifically recognizes a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ ID No. 290 when bound to an MHC molecule, the a T-cell receptor or fragment thereof according to claim 7 or 8 that is reactive with an HLA ligand, wherein said ligand is a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ ID No. 290 when bound to an MHC molecule, or the a nucleic acid or the an expression vector according to claim 11, expressing said nucleic acid, wherein the nucleic acid encodes for said peptide, antibody, or T-cell receptor, wherein said host cell preferably optionally is selected from an antigen presenting cell, such as a dendritic cell, a T cell or an NK cell.~~

in the manufacture of a medicament against prostate cancer.

~~13. 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 3.~~

~~14.9. Use of A~~an activated T lymphocyte, produced by the method according to claim 13,
that selectively recognizes a cell which over-presents a polypeptide comprising an
amino acid sequence given in any one of claims 1 to 3 consisting of SEQ ID No.
290, in the manufacture of a medicament against prostate cancer.

~~15.10. Use of A~~a pharmaceutical composition comprising at least one active ingredient
selected from the group consisting of the pharmaceutically acceptable salt
according to claim 1 or claim 2, a peptide consisting of SEQ ID No. 290 according to
any one of claims 1 to 5, thean antibody or fragment thereof that specifically
recognizes a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ
ID No. 290 when bound to an MHC molecule according to claim 6, thea T-cell
receptor or fragment thereof that is reactive with an HLA ligand, wherein said ligand
is a peptide consisting of SEQ ID No. 290, or the peptide consisting of SEQ ID No.
290 when bound to an MHC molecule according to claim 7 or 8, the aptamer
according to claim 10, thea nucleic acid or the an expression vector expressing said
nucleic acid, wherein the nucleic acid encodes for said peptide, antibody, or T-cell
receptor according to claim 11, thea host cell comprising said peptide, antibody, T-
cell receptor, or nucleic acid or expression vector according to claim 12, or thean
activated T lymphocyte that specifically recognizes a cell which over-presents a
peptide consisting of SEQ ID No. 290 according to claim 14, or a conjugated or
labelled active ingredient, and a pharmaceutically acceptable carrier, and optionally,
pharmaceutically acceptable excipients and/or stabilizers,
in the manufacture of a medicament against prostate cancer.

11. The use according to claim 10, further comprising one or more adjuvants selected
from interleukin and immunoadjuvant.

12. The use according to claim 11, wherein
a) the interleukin is IL-2; and/or
b) the immunoadjuvant is IL-15.

- ~~16. A method for producing the peptide or variant thereof according to any of claims 1 to 6, the antibody or fragment thereof according to claim 6, or the T-cell receptor or fragment thereof according to claim 7 or 8, the method comprising culturing the host cell according to claim 12, and isolating the peptide or variant thereof, the antibody or fragment thereof or the T-cell receptor or fragment thereof from said host cell and/or its culture medium.~~
- ~~17. The peptide according to any one of claims 1 to 5, the antibody or fragment thereof according to claim 6, the T-cell receptor or fragment thereof according to claim 7 or 8, the aptamer according to claim 10, the nucleic acid or the expression vector according to claim 11, the host cell according to claim 12, or the activated T lymphocyte according to claim 14 for use in medicine.~~
- ~~18.13. 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 3, the method comprising administering to the patient Use of an effective number of activated T cells as defined in claim 14 that specifically recognize a cell which over-presents a peptide consisting of SEQ ID No. 290 in the manufacture of a medicament for killing target cancer cells which over-present a peptide consisting of SEQ ID No. 290.~~
- ~~19.14. Use of Tthe pharmaceutically acceptable salt according to claim 1 or claim 2 peptide according to any one of claims 1 to 5, the antibody or fragment thereof according to claim 6, the T-cell receptor or fragment thereof according to claim 7 or 8, the aptamer according to claim 10, the nucleic acid or the expression vector according to claim 11, the host cell according to claim 12, or the activated T lymphocyte according to claim 14 for use in diagnosis and/or treatment of cancer, or for use in the manufacture of a medicament against cancer.~~
- ~~20.15. The use according to claim 19 any one of claims 3 to 14, wherein said cancer is selected from the group of acute myeloid leukemia, breast cancer, cholangiocellular carcinoma, chronic lymphocytic leukemia, colorectal cancer, gallbladder cancer, glioblastoma, gastric cancer, hepatocellular carcinoma, head and neck squamous~~

cell carcinoma, melanoma, non-Hodgkin lymphoma, lung cancer (including non-small cell lung cancer adenocarcinoma, squamous cell non-small cell lung cancer, and small cell lung cancer), ovarian cancer, esophageal cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, urinary bladder carcinoma, uterine and endometrial cancer and other tumors that show an overexpression ~~over-~~presentation of a protein from which a peptide consisting of SEQ ID NO: 290, SEQ ID NO: 1 to SEQ ID NO: 251, SEQ ID NO: 289 and SEQ ID NO: 291 is derived from.

21. ~~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 5, the antibody or fragment thereof according to claim 6, the T-cell receptor or fragment thereof according to claim 7 or 8, the aptamer according to claim 10, the nucleic acid or the expression vector according to claim 11, the host cell according to claim 12, or the activated T lymphocyte according to claim 14, 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: 290, SEQ ID NO: 1 to SEQ ID NO: 286, SEQ ID NO: 289 and SEQ ID NO: 291, and~~
- ~~d) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.~~

22. ~~The kit according to claim 21, further comprising one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle, or (vii) a syringe.~~

23. 16. A method for producing a personalized anti-cancer vaccine or a compound-based and/or cellular ~~therapy~~ therapeutic agent for an individual ~~patient~~, 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 tumor sample of said individual patient; and

d) manufacturing and/or formulating the personalized vaccine or compound-based or cellular ~~therapy~~ therapeutic agent based on step c);

wherein the selected warehouse peptide is a peptide consisting of SEQ ID No. 290.

~~24-~~17. The method according to claim ~~23-16~~, 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.

~~25-~~18. The method according to claim ~~23-16~~ or ~~24-17~~, 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.

~~26-~~19. The method according to any of claims ~~23-16~~ to ~~25-18~~, wherein the normal tissue corresponding to the tissue type of the tumor sample is obtained from the same patient.

~~27-~~20. The method according to any of claims ~~23-16~~ to ~~26-19~~, 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~~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 ~~patient~~individual.

~~28-21.~~ The method according to any of claims ~~23-16~~ to ~~27~~20, 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.

~~29.~~ The method according to any of claims ~~23 to 28~~, wherein said warehouse comprises a plurality of peptides selected from the group consisting of SEQ ID NO: 290, SEQ ID NO: 1 to SEQ ID NO: 286, SEQ ID NO: 289 and SEQ ID NO: 291.

~~30-22.~~ The method according to any of claims ~~23-16~~ to ~~29~~21, 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.

~~31-23.~~ The method according to claim ~~30~~22, wherein said at least one mutation is identified by whole genome sequencing.