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Antitumor immunterápia

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Description

[0001] The present invention relates to the use of telomerase-derived peptides for the treatment of any cancer patients, particularly for the treatment of patients with renal or prostate cancer.

[0002] Renal cell carcinoma (RCC) represents the 3% of tumors in adults and its incidence increases at a rate of 1.5-5.9% per year. The mortality rate for this disease is increasing proportionally to the augment of incidence. About 25-30% of patients has advanced, metastatic disease at diagnosis, and several patients without clinical evidence of metastasis at the time of diagnosis have already disseminated micrometastases. This is responsible for the poor efficacy of actual therapeutic approaches and for the low survival rates (0-13% of metastatic patients survive after 5 years from diagnosis).

[0003] Prostate cancer is a major medical problem. In Europe there are 2.6 millions of new cases every year. It constitutes the 11 % of tumor cases in males, and it is responsible for the 9% of deaths due to cancer in Europe. Moreover, its incidence in male population is the double of that of lung cancer; prostate cancer constitutes the 30% of new neoplasia cases in males with a elevated mortality rate.

[0004] At diagnosis the 45% of patients has already an advanced disease with a survival rate < 50% at five years independently from the type of therapeutic approach.

[0005] Telomerase is the reverse transcriptase of eukaryotic cells required for the synthesis of the telomeric regions of chromosomes. Telomerase is present in embryonic but not in adult somatic cells with few exceptions constituted by germinal cells and actively proliferating cells. However, the rate of telomerase expression in these cells is so low that telomerase cannot be recognized by telomerase-specific cytotoxic lymphocytes (CTL). Telomerase is essential for cell immortalization: this explains why it is expressed by about 90% of tumours (independently on the histological type). For this reason, telomerase is now considered a potential "universal" tumor antigen. This view is further supported by the finding that cytotoxic T lymphocytes (CTL) able to kill cancer cells through the specific recognition of peptides derived from the catalytic subunit of the human telomerase reverse transcriptase (hTERT) have been identified in the peripheral blood of both healthy subjects and cancer patients. In particular, about 90% of cancer patients have telomerase-specific CTL.

[0006] On this basis, clinical trials have been performed (or are ongoing) to analyze the safety and the immunological effects of immunization of cancer patients with single telomerase peptides or a combination of 2 telomerase peptides. These trials have demonstrated that telomerase immunization is a safe procedure. In particular, no toxicity on hematopoietic stem cells has been detected (Vonderheide RH, et al. Vaccination of cancer patients against telomerase induces functional antitumor CD8+ T lymphocytes. Clin Cancer Res 2004; 10:828-839.

Danet-Desnoyers GH, et al. Telomerase vaccination has no detectable effect on SCID-repopulating and colony-forming activities in the bone marrow of cancer patients. Exp Hematol 2005;33:1275-1280. Brunsvig PF, et al. Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer. Cancer Immunol Immunother. 2006;55:1553-1564). Further telomerase-specific immune responses were induced in several cancer patients. However, although different experimental approaches have been applied partial or complete clinical responses have been obtained only in a minority of treated patients.

[0007] The present inventors have now found that an accurate selection of immunogenic peptides and an efficient adjuvant are mandatory for the development of efficient telomerase peptide-based immunotherapy protocol. According to the present invention, a composition comprising a plurality of telomerase-derived peptides is administered for presentation by antigen-presenting cells. This composition comprises both HLA class I and HLA class II restricted peptides. The availability of telomerase epitopes restricted by HLA class I or II molecules and, hence, recognized by CD8+ or CD4+ T lymphocytes, respectively, has great importance since provide the chance to design protocol of active immunization potentially mimicking a fully physiological immune response. In fact, it has been demonstrated that an immune response characterized by the activation not only of tumour-specific CTL but also of tumour-specific CD4+ T cells is essential to achieve efficient anti-tumour effects. This is due to the fact that CD4+ T cells are responsible for processes of induction, regulation and maintenance of CTL-mediated immune responses, as well as of direct anti-tumour killing. A molecular feature of telomerase-derived epitopes restricted by HLA class II molecules is their promiscuity, that is their capacity to bind and be presented by different HLA class II alleles. This is a great advantage in designing an immunotherapeutic protocol since it allows that single peptide epitopes may be efficiently used to immunize individuals bearing different HLA haplotypes. Thus, a great number of patients might be responsive to immunization with a suitable combination of telomerase-derived peptides.

[0008] The present invention is defined by the claims.

[0009] In a first aspect, the present disclosure refers to a composition of at least 3 peptides from a mammalian telomerase, particularly from human telomerase, comprising:

- (i) at least one HLA class I restricted peptide and
- (ii) at least two HLA class II restricted peptides.

[0010] The peptide composition of the present disclosure comprising the invention comprises at least four peptides, e.g. four, five or even more peptides. Preferably, the composition comprises four peptides. More preferably, the composition comprises one HLA class I restricted peptide and at least two, particularly at least three

HLA class II restricted peptides. The HLA class I restricted peptide is preferably a HLA-A2 restricted peptide. The HLA class II restricted peptides are preferably HLA-DR1, -DR4, -DR7, -DR15, -DP4 and -DQ4 restricted peptides. HLA class I restricted peptides preferably have a length of 7 to 11 amino acids, e.g. 9 amino acids, and HLA class II restricted peptides preferably have a length of 12 to 18 amino acids, e.g. 15 amino acids.

[0011] Preferably the peptides of the composition are present in a single container. The amount of each peptide in the composition is usually of from 100-1000 µg, preferably from 200-800 µg, and more preferably from 400-600 µg. Most preferably, each peptide is present in about the same amount e.g. in an amount of about 500 µg.

[0012] The HLA class I restricted peptide (i) preferably comprises the amino acid sequence ILAKF LHWL (SEQ ID NO:1) corresponding to amino acids 540-548 of human telomerase. However, any telomerase-derived peptide able to bind to any gene product of an HLA class I allele and to induce activation of peptide-specific CTLs is to be considered suitable for the specific use included in the present disclosure. The HLA class II restricted peptides (i) are preferably selected from peptides comprising the amino acid sequences RPGLL GASVL GLDDI (SEQ ID NO:2) corresponding to amino acids 672-686 of human telomerase, LTDLQ PYMRQ FVAHL (SEQ ID NO:3) corresponding to amino acids 766-780 of human telomerase, and EARPA LLTSRLRFIPK (SEQ ID NO:4) corresponding to amino acids 611-626 of human telomerase. However, any telomerase-derived peptide able to bind to any gene product of any HLA class II allele and to induce activation of peptide-specific CD4⁺ T lymphocytes is to be considered suitable for the specific use included in the present disclosure.

[0013] The peptides may be synthesized according to known methods, e.g. by solid phase synthesis techniques. If desired, the peptides may comprise N- and/or C-terminal modifications such as acylation or amidation.

[0014] In an embodiment of the invention, the peptide composition is administered in combination with an adjuvant capable of interacting with toll-like receptors (TLRs) and providing a pro-inflammatory support, wherein the adjuvant is imiquimod in another instance of the disclosure, the adjuvant is an imidazoquinoline derivative which binds to TLR7 and 8 on human dendritic cells inducing maturation of these cells toward antigen presentation by increasing expression of HLA and co-stimulatory molecules, increasing expression of chemokine receptors such as CCR7 and/or inducing secretion of Th1 cytokines such as IFN γ , IN12 or TFN α . Further preferred adjuvants are agents binding to and/or activating TLRs, such as CpG-containing oligonucleotides. Moreover, the additional use of compounds, such as Montanide ISA-51, able to reduce the clearance of administered peptides at the site of injection and to exert adjuvant activity, is also part of the disclosure.

[0015] The composition of the present invention is suit-

able for use in medicine, particularly in human medicine, more particularly as a vaccine for cancer. The composition is useful for the vaccination against any cancer which is telomerase positive. Preferred examples are renal cancer, e.g. renal cell carcinoma, prostate cancer, e.g. prostate adenocarcinoma, but also lung, breast, ovary cancers and lymphomas. The cancer may be in any stage, e.g. in an early stage or in an advanced stage, e.g. at least stage IV.

[0016] In a preferred embodiment, the composition is used for administration to a HLA matched human patient, i.e. a human patient who is positive for HLA alleles which correspond to the HLA class I or II alleles which restrict presentation to T lymphocytes of peptides (i) and/or (ii). Especially preferred is an administration to a patient who has been tested to be positive for the HLA-A2 allele corresponding to the preferred HLA class I restricted peptide (i) comprising SEQ ID NO:1.

[0017] The composition of the present invention is administered by any suitable route, e.g. by injection, more particularly by intradermal injection. In order to enhance the immune response, the composition of the disclosure comprising the invention is administered together with an adjuvant, e.g. imiquimod.

[0018] Further, it is preferred to administer the composition by a protocol comprising a plurality of subsequent administrations, e.g. five or more subsequent administrations. In an especially preferred instance, the composition is for administration by a protocol comprising:

- 1st week: 2-4 times administration, preferably 3 times administration at intervals of about 48 hours,
- 2nd-4th week: 1-2 weekly administrations, preferably 1 weekly administration,
- 5th-7th week: 1 administration, preferably 6th week 1 administration,
- 9th-12th to 12th week: 1 administration, preferably 10th week 1 administration.

[0019] Before and after each administration, the adjuvant, e.g. imiquimod, is preferably spread at the administration site for e.g. at least 30 seconds to allow its action.

[0020] The administered dose preferably comprises each peptide in about equal amounts, e.g. of about 500 µg.

[0021] Further, the present invention is explained in more detail by the following example.

Example**Phase III/III Clinical Trial for the Treatment of Patients with Stage IV renal or prostate cancer****1. Inclusion criteria for patients affected with prostate cancer****[0022]**

- Histologic diagnosis of prostate adenocarcinoma
- Resistance to hormonal therapy defined as progression after 4 week treatment
- Stage IV of disease
- PSA > 10 microg/ml increasing in the last month
- Acceptable liver function defined as: total bilirubin < UNL ("upper normal limit"), AST and ALT < 2.5 x UNL, alkaline phosphatase < 5 x UNL
- Acceptable renal function defined as: serum creatinine < 1,5 x UNL
- Acceptable hematopoietic function defined as: hemoglobin > 7 g/l, leukocytes > 3 x 10⁹/l, platelets > 100 x 10⁹/l
- Positivity for the HLA-A2 allele
- ECOG performance status < 3
- Life expectancy > 3 months
- Absence of coexisting immunosuppressive or chemotherapeutic therapy since 30 days before study onset
- Absence of coexisting autoimmune diseases
- The patient must be able to adhere to protocol requests
- The patient must provide written informed consent
- Age > 18 years

2. Inclusion criteria for patients affected with renal cancer**[0023]**

- Histologic diagnosis of renal cell carcinoma
- Normal renal function of the non-affected kidney
- Acceptable liver function defined as: total bilirubin < UNL ("upper normal limit"), AST and ALT < 2.5 x UNL, alkaline phosphatase < 5 x UNL
- Acceptable hematopoietic function defined as: hemoglobin > 7 g/l, leukocytes > 3 x 10⁹/l, platelets > 100 x 10⁹/l
- Positivity for the HLA-A2 allele
- ECOG performance status < 3
- Life expectancy > 3 months
- Male patient
- Female patient not pregnant, not breast feeding and under efficient contraceptive therapy
- Absence of coexisting immunosuppressive or chemotherapeutic therapy since 30 days before study onset
- Absence of coexisting autoimmune diseases
- The patient must be able to adhere to protocol re-

quests

- The patient must provide written informed consent
- Age > 18 years

3. Treatment protocol**3.1 Telomerase derived peptides**

[0024] The following immunogenic, telomerase-derived peptides are employed in the study:

hTERT540-548 (sequence: ILAKFLHWL; restriction: HLA-A2);
 hTERT672-686 (sequence: RPGLLGASVLGLDDI; restriction: HLA-DR1, DR7, DR15);
 hTERT766-780 (sequence: LTDLPYMRQFVAHL; restriction: HLA-DR4, DR7, DR15);
 hTERT611-626 (sequence: EARPALLTSRLRFIPK; restriction: HLA-DP4, DQ4).

3.2 Group composition

[0025] Two groups of patients will be constituted, one for each histologic type of disease. Ten patients per group will be enrolled.

3.3 Treatment

[0026] Patients will be treated by active immunotherapy through intradermic injection of the above cited telomerase-derived peptides. A pool of the 4 different peptides will be administered with each injection (500 µg of each peptide per injection). The total injected volume will be 0.4 ml.

[0027] Treatment schedule will be as follows:

1st week: 3 intradermic injections at intervals of 48 hours;
 2nd-4th weeks: 1 weekly injection;
 6th week: 1 injection;
 10th week: 1 injection.

Before and after each injection imiquimod (commercial name: Aldara) will be spread at the injection site for 30 seconds to allow its absorption.

Claims

1. A composition of 4 peptides from a mammalian telomerase, comprising:

- (i) one HLA class I restricted peptide and
 - (ii) three HLA class II restricted peptides
- in combination with an adjuvant, wherein:

- (a) said one HLA class I restricted peptide is ILAKF LHWL (SEQ ID NO:1),
- (b) said three HLA class II restricted pep-

- tides are respectively RPGLL GASVL GLDDI (SEQ ID NO:2), LTDLQ PYMRQ FVAHL (SEQ ID NO:3), and EARPA LLTSRLRFIPK (SEQ ID NO:4),
(c) said adjuvant is capable of interacting with toll-like receptors (TLR) and wherein said adjuvant is imiquimod.
2. The composition of claim 1 wherein said telomerase is human.
 3. The composition according to any one of claims 1 and 2 for use in medicine.
 4. The composition according to any one of claims 1 and 2 for use in human medicine.
 5. The composition for the use according to anyone of claims 3 and 4 as a vaccine for renal or prostate cancer.
 6. The composition for the use according to claim 5 wherein said renal or prostate cancer is advanced.
 7. The composition according to any one of claims 1 and 2, suitable for administration by intradermal injection.

Patentansprüche

1. Zusammensetzung von 4 Peptiden aus einer Säugtier-Telomerase, umfassend:
 - (i) ein HLA Klasse-I restringiertes Peptid und
 - (ii) drei HLA Klasse-II restringierte Peptide in Kombination mit einem Hilfsstoff, wobei:
 - (a) das HLA Klasse-I restringierte Peptid ILAKF LHWL (SEQ ID NO:1) ist,
 - (b) die drei HLA Klasse-II restringierten Peptide jeweils RPGLL GASVL GLDDI (SEQ ID NO:2), LTDLQ PYMRQ FVAHL (SEQ ID NO:3) und EARPA LLTSRLRFIPK (SEQ ID NO:4) sind,
 - (c) der Hilfsstoff in der Lage ist, mit Toll-ähnlichen Rezeptoren (TLR) zusammenzuwirken und wobei der Hilfsstoff Imiquimod ist.
2. Zusammensetzung nach Anspruch 1, wobei die Telomerase menschliche Telomerase ist.
3. Zusammensetzung nach einem der Ansprüche 1 und 2 zur medizinischen Verwendung.
4. Zusammensetzung nach einem der Ansprüche 1 und 2 zur humanmedizinischen Verwendung.

5. Zusammensetzung zur Verwendung nach einem der Ansprüche 3 und 4 als Impfstoff gegen Nieren- oder Prostatakrebs.

6. Zusammensetzung zur Verwendung nach Anspruch 5, wobei der Nieren- oder Prostatakrebs sich im fortgeschrittenen Stadium befindet.

7. Zusammensetzung nach einem der Ansprüche 1 und 2, geeignet für die Verabreichung mit intradermaler Injektion.

Revendications

1. Composition de 4 peptides à partir d'une télomérase mammifère, comprenant :

- (i) un peptide restreint HLA de classe I, et
- (ii) trois peptides restreints HLA de classe II en combinaison avec un adjuvant, dans laquelle :

(a) ledit un peptide restreint HLA de classe I est ILAKF LHWL (SEQ ID N°1),

(b) lesdits trois peptides restreints HLA de classe II sont respectivement RPGLL GASVL GLDDI (SEQ ID N° 2), LTDLQ PYMRQ FVAHL (SEQ ID N° 3), et EARPA LLTSRL RFIPK (SEQ ID N° 4),

(c) ledit adjuvant est capable d'interagir avec des récepteurs de type Toll (TLR) et dans laquelle ledit adjuvant est l'imiquimod.

2. Composition selon la revendication 1, dans laquelle ladite télomérase est humaine.

3. Composition selon l'une quelconque des revendications 1 et 2, destinée à être utilisée en médecine.

4. Composition selon l'une quelconque des revendications 1 et 2, destinée à être utilisée en médecine humaine.

5. Composition pour l'usage selon l'une quelconque des revendications 3 et 4, comme un vaccin pour le cancer du rein ou de la prostate.

6. Composition pour l'usage selon la revendication 5, dans laquelle ledit cancer du rein ou de la prostate est avancé.

7. Composition selon l'une quelconque des revendications 1 et 2, adapté pour l'administration par injection intradermique.

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

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- **BRUNSVIG PF et al.** Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer. *Cancer Immunol Immunother*, 2006, vol. 55, 1553-1564 [0006]



Antitumor immunterápia

SZABADALMI IGÉNYPONTOK

1. Készítmény egy emlős telomerázból származó 4 peptidből, amely tartalmaz:

- (i) egy HLA I osztályú resztrikciós peptidet és
- (ii) három HLA II osztályú resztrikciós peptidet egy adjuvánssal való kombinációban, ahol

(a) a HLA I osztályú resztrikciós peptid az ILAKF LHWL (SEQ ID NO:1),

(b) a három HLA II osztályú resztrikciós peptid az RPGLL GASVL GLDDI (SEQ ID NO:2), LTDLQ PYMRQ FVAHL (SEQ ID NO:3), illetőleg EARPA LLTSRLRFIPK (SEQ ID NO:4),

(c) az adjuváns képes toll-szerű receptorokkal (TLR) való interakcióra, és az adjuváns imiquimod.

2. Az 1. igénypont szerinti készítmény, ahol a telomeráz humán telomeráz.

3. Az 1. vagy 2. igénypont szerinti készítmény orvoslásban való alkalmazásra.

4. Az 1. vagy 2. igénypont szerinti készítmény humán orvoslásban való alkalmazásra.

5. A 3. és 4. igénypontok egyike szerinti alkalmazásra szolgáló készítmény vese- vagy prosztata-rák elleni vakcinaként.

6. Az 5. igénypont szerinti alkalmazásra szolgáló készítmény, ahol a vese- vagy prosztata-rák előrehaladott.

7. Az 1. vagy 2. igénypont szerinti készítmény, amely alkalmas intradermális injektálásra.

A meghatalmazott:

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