present antigens and initiate an immune response (Steinman, R., Banchereau, J. Nature 449, 419–426 (2007)). Mature DCs migrate to the draining lymph node and where they present the antigen-derived short peptides at the surface through Major Histocompatibility Complex (MHC) molecules. Antigen-specific T cells present in the lymph nodes can then interact with peptide-MHC complexes through TCR (T Cell Receptor). The recognition of peptide-MHC by specific TCR in conjunction with co-stimulatory signals, initiates T cell activation (Steinman, R., Banchereau, J. Nature 449, 419–426 (2007)).

The aim of the present invention is to provide therapeutic and prophylactic vaccines for the prevention and treatment of HPV-induced cancers.

Therapeutic vaccination against high-risk human papillomaviruses with an integrase defective lentiviral vector expressing non-oncogenic HPV16 E7 fused to calreticulin (CRT) has been described (Grasso *et al.,* Int J Cancer. 2013 Jan 15;132(2):335-44). The tests were performed against early-stage tumors and showed the ability of this construct to eradicate said tumors in a reasonable but not perfect number of vaccinated mice.

Accordingly, there is still a need in the art for the treatment of more aggressive and/or well implanted tumors induced by HPV, which are known in the art as being more difficult to eliminate than small and early-stage tumors.

There is also a need for a treatment of resistant tumors induced by HPV, i.e. tumors characterized in that they are strongly infiltrated with Regulatory T cells (Tregs).

There is moreover a need for a therapeutic vaccine allowing infiltration with $CD8^+$ and $CD4^+$ cells in HPV-induced tumors to be treated while reducing Tregs in said tumors.

There is also a need for the generation of a strong immunological memory against HPV and in particular against PDHPV antigens, more particularly against HPV16 and HPV18 antigens.

There is also a need for the generation of a novel safe, non-oncogenic, prophylactic and therapeutic vaccine against HPV induced cancers.

There is further a need for a vaccine allowing, after administration of a single dose, to fully eliminate primary tumors and to provide a strong protection against relapse.

The invention has for purpose to meet the above-mentioned needs.

SUMMARY

The present disclosure accordingly relates to the following items:

administration of the said vaccine composition, lentiviral vector, lentiviral vector particle or cell.

In one aspect, the present disclosure refers to the use of the vaccine composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of an HPV induced cancer, in particular selected from the group consisting of cervical cancer, vaginal cancer, vulvar cancer, penile cancer, anal cancer, oropharyngeal cancer, and metastases thereof, in particular pulmonary metastasis thereof. In another aspect, the present disclosure refers to the use of the lentiviral vector, lentiviral vector particle or cell as disclosed herein, in the manufacture of a medicament for the treatment or prevention of an HPV induced cancer, in particular selected from the group consisting of cervical cancer, vaginal cancer, vulvar cancer, penile cancer, anal cancer, oropharyngeal cancer, and metastases thereof, in particular pulmonary metastasis thereof.

The details, examples and preferences provided in relation to any particular one or more of the stated aspects of the present disclosure will be further described herein and apply equally to all aspects of the present invention. Any combination of the embodiments, examples and preferences described herein in all possible variations thereof is encompassed by the present disclosure unless otherwise indicated herein, or otherwise clearly contradicted by context.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 demonstrates that HPV vaccines of the invention are immunogenic *in vivo*. Mice were injected i.m. with $1x10^7$TU of lentiviral vector particles comprising the lentiviral vector filed at the CNCM under accession number I-5759, the lentiviral vector filed at the CNCM under accession number I-5760, the lentiviral vector filed at the CNCM under accession number I-5761 or the lentiviral vector filed at the CNCM under accession number I-5762 or 50 µL of diluent. 14 days later, splenocytes were prepared and restimulated overnight for IFNg ELISPOT with 4 distinct peptide pools.

Abscissa: from left to right: results obtained with the lentiviral vector filed at the CNCM under accession number I-5759, the lentiviral vector filed at the CNCM under accession number I-5760, the lentiviral vector filed at the CNCM under accession number I-5761, the

lentiviral vector filed at the CNCM under accession number I-5762 or with 50 µL of diluent (control).

Ordinate: Spot Forming Cells (SFC)/10^6 cells.

Figure 2 shows that invention vaccine fully eliminates well implanted tumors *in vivo*. TC-1 cells were injected s.c. and tumor volume was measured every other day (caliper measurement). When average tumor volume is 70 mm^3, mice were randomized and vaccinated with $1x10^8$ TU i.m. of LV-GFP Indiana (as a control), Indiana lentiviral vector particles comprising I-5759, Indiana lentiviral vector particles comprising I-5760, Indiana

CLAIMS

1. A lentiviral vector, in particular a non-integrative lentiviral vector, comprising at least four distinct nucleic acid sequences selected from the group consisting of:

- at least one nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen,
- at least one nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen,
- at least one nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen, and
- at least one nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen.

2. The lentiviral vector according to claim 1, wherein the nucleic acid sequence encoding the non-oncogenic Human papillomavirus (HPV16) protein E6 antigen encodes an amino acid sequence having at least 80% sequence identity with the amino acid sequence set forth as SEQ ID NO: 7, the nucleic acid sequence being in particular selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.

3. The lentiviral vector according to claim 1 or 2, wherein the nucleic acid sequence encoding the non-oncogenic Human papillomavirus (HPV16) protein E7 antigen encodes an amino acid sequence having at least 68% sequence identity with the amino acid sequence set forth as SEQ ID NO: 16, the nucleic acid sequence being in particular selected from the group consisting of SEQ ID NO: 14 and SEQ ID NO: 15.

4. The lentiviral vector according to any one of claims 1 to 3, wherein the nucleic acid sequence encoding the non-oncogenic Human papillomavirus (HPV18) protein E6 antigen encodes an amino acid sequence having at least 60% sequence identity with the amino acid sequence set forth as SEQ ID NO: 24**,** the nucleic acid sequence being in particular selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 23.

5. The lentiviral vector according to any one of claims 1 to 4, wherein the nucleic acid sequence encoding the non-oncogenic Human papillomavirus (HPV18) protein E7 antigen

encodes an amino acid sequence having at least 83% sequence identity with the amino acid sequence set forth as SEQ ID NO: 33, the nucleic acid sequence being in particular selected from the group consisting of SEQ ID NO: 30, SEQ ID NO: 31 and SEQ ID NO: 32.

6. The lentiviral vector according to any one of claims 1 to 5, wherein the at least four distinct nucleic acid sequences encoding antigens are fused together, forming a single antigenic nucleic acid sequence encoding a single antigenic fusion protein under the control of a single promoter sequence.

7. The lentiviral vector according to any one of claims 1 to 6, wherein the order of the at least four distinct nucleic acid sequences, from 5' end to 3' end, is selected from the group consisting of:

(a) nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen;

(b) nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen;

(c) nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen; and

(d) nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen.

8. The lentiviral vector according to any one of claims 1 to 7, wherein the order of the at least four distinct nucleic acid sequences, from 5' end to 3' end, is (a) nucleic acid

sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV16) protein E6 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E7 antigen - nucleic acid sequence encoding a non-oncogenic Human papillomavirus (HPV18) protein E6 antigen.

9. The lentiviral vector according to any one of claims 1 to 8, comprising a nucleic acid sequence which encodes an amino acid sequence having at least 90% sequence identity with the amino acid sequence set forth as SEQ ID NO: 42, the nucleic acid sequence being in particular the nucleic acid sequence SEQ ID NO: 41.

10. The lentiviral vector according to any one of claims 1 to 9, being selected from the group consisting of the non-integrative lentiviral vectors filed at the CNCM under accession numbers I-5759, I-5760, I-5761 and I-5762, and is in particular the non-integrative lentiviral vector filed at the CNCM under accession number I-5759.

11. The lentiviral vector according to any one of claims 1 to 10, wherein the lentiviral vector comprises a MHC Class I promoter, and in particular a β2-microglobulin promoter.

12. The lentiviral vector according to any one of claims 1 to 11, wherein the lentiviral vector comprises a cPPT/CTS sequence, in particular the cPPT/CTS sequence set forth as sequence SEQ ID NO: 37.

13. The lentiviral vector according to any one of claims 1 to 12, wherein the lentiviral vector comprises a 3' long terminal repeat (LTR) which is devoid of its U3 promoter sequence.

14. The lentiviral vector according to any one of claims 1 to 13, wherein the lentiviral vector does not comprise a constitutive enhancer sequence.

15. The non-integrative lentiviral vector according to any one of claims 1 to 14, wherein the lentiviral vector comprises a mutant form of the woodchuck hepatitis B virus (WHV) post-transcriptional regulatory element (WPRE), and in particular having the sequence set forth as sequence SEQ ID NO: 38.

16. A lentiviral vector particle, in particular a non-integrative lentiviral vector particle, comprising at least one lentiviral vector as defined in any one of claims 1 to 15.

17. The lentiviral vector particle according to claim 16, wherein the lentiviral vector particle comprises a functional lentiviral integrase protein.

18. The lentiviral vector particle according to claim 16 or 17, wherein the lentiviral vector particle comprises a vesicular stomatitis virus glycoprotein (VSVG), in particular a VSV-G Indiana serotype or a VSV-G New Jersey serotype.

19. The lentiviral vector particle according to any one of claims 16 to 18, wherein the lentiviral vector particle comprises HIV-1 subtype D Gag and Pol proteins.

20. An isolated cell comprising the lentiviral vector according to any one of claims 1 to 15 or the lentiviral vector particle according to any of claims 16 to 19.

21. A vaccine composition comprising a lentiviral vector according to any one of claims 1 to 15, a lentiviral vector particle according to any one of claims 16 to 19, or a cell according to claim 20.

22. Use of the vaccine composition according to claim 21, in the manufacture of a medicament for the treatment or prevention of an HPV induced cancer, in particular selected from the group consisting of cervical cancer, vaginal cancer, vulvar cancer, penile cancer, anal cancer, oropharyngeal cancer, and metastases thereof, in particular pulmonary metastasis thereof.

23. A lentiviral vector according to any one of claims 1 to 15, a lentiviral vector particle according to any one of claims 16 to 19, or a cell according to claim 20, for use as a medicament or vaccine.

24. Use of the lentiviral vector, lentiviral vector particle or cell, according to claim 23, in the manufacture of a medicament for the treatment or prevention of an HPV induced cancer, in particular selected from the group consisting of cervical cancer, vaginal cancer, vulvar cancer, penile cancer, anal cancer, oropharyngeal cancer, and metastases thereof, in particular pulmonary metastasis thereof.

25. The use of claim 22 or claim 24, or the lentiviral vector, lentiviral vector particle or cell for use according to claim 23, wherein said vaccine composition, lentiviral vector, lentiviral vector particle or cell is to be administered in combination with at least one immune checkpoint inhibitor, in particular at least one monoclonal antibody selected from the group

consisting of anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-NKG2A, anti-TIM-3, anti-TIGIT and anti-LAG-3 monoclonal antibodies and more particularly with at least one anti-PD-1 monoclonal antibody.

26. The use of claim 25 or the lentiviral vector, lentiviral vector particle or cell for use according to claim 25, wherein the at least one immune checkpoint inhibitor is to be administered simultaneously or separately, and in particular the at least one immune checkpoint inhibitor is to be administered at least 2, and in particular at least 4 days after the administration of the said vaccine composition, lentiviral vector, lentiviral vector particle or cell.