# COMBINATION THERAPY ~~WITH OMOMYC AND AN ANTIBODY BINDING PD-1 OR CTLA-4~~ FOR THE TREATMENT OF CANCER

## FIELD OF THE INVENTION

The present invention relates to the field of cancer and, more particularly, to a combination comprising polypeptides and immuno-oncology agents and its use in medicine, more particularly in the prevention and/or treatment of cancer.

## BACKGROUND OF THE INVENTION

The ideal cancer drug should target a non-redundant function continuously necessary for tumor maintenance, but dispensable for maintenance and function of any normal tissues. Hence, the most common logic is to target gene products that are specifically mutated in cancer, on the basis that these mutant molecules would be the likely "drivers" of the cancer and, perhaps, less critical for normal tissues. For these reasons, much attention has focused on cataloguing recurring lesions in specific cancer types. Unfortunately, there are several problems to this approach. First, most solid human cancers pass through episodes of genomic instability and exhibit a mutational noise that can obscure the "driver" mutations and their attendant effector pathways. Second, cancers are the end result of a process that involves transitions through multiple evolutionary bottlenecks. Each bottleneck may require a specific type of mutation whose function is thereafter dispensable for tumor maintenance and, consequently, not a good therapeutic target after that point in the tumor's evolution.

Myc is a basic helix-loop-helix leucine zipper (b-HLH-LZ) protein involved in growth control and cancer, which operates in a network with the structurally related proteins Max, Mad and Mnt. Myc/Max dimers activate gene transcription and induce cell proliferation or apoptosis. Mad/Max and Mnt/Max complexes act as repressors and cause cell growth arrest and differentiation. All dimers recognize the same DNA consensus site, the CACGTG E-box.

Myc is tightly regulated in normal cells, where its levels are higher in proliferating and lower in non-proliferating cells. Aberrantly high and/or deregulated Myc activity is causally implicated in most cancers and often associated with aggressive, poorly differentiated and angiogenic tumors. The deregulation of Myc expression is due to overexpression through gene amplifications, loss of transcriptional control, impaired degradation or increased stabilization. This results in aberrant proliferation, increased

## CLAIMS

1. A combination comprising:

i) a first component selected from the group consisting of:

a) a polypeptide comprising the sequence SEQ ID NO: 1 or a functionally equivalent variant thereof,

b) a conjugate comprising a polypeptide comprising the sequence SEQ ID NO: 1 or a functionally equivalent variant thereof and a chemical moiety that facilitates cellular uptake of the polypeptide or of the functionally equivalent variant thereof,

c) a polynucleotide encoding the polypeptide of a) or the conjugate of b),

d) a vector comprising the polynucleotide according to c), and

e) a cell capable of secreting into the medium the polypeptide according to a) or the conjugate according to b),

wherein the functionally equivalent variant of SEQ ID NO: 1 is a polypeptide having a threonine at the position corresponding to position 61 of SEQ ID NO: 1, an isoleucine at the position corresponding to position 68 of SEQ ID NO: 1, a glutamine at the position corresponding to position 74 of SEQ ID NO: 1 and an asparagine at the position corresponding to position 75 of SEQ ID NO: 1, and having a degree of identity with respect to SEQ ID NO: 1 greater than 70%;

and

ii) a second component that is an immuno-oncology agent, wherein the immuno-oncology agent is a PD-1 antagonist or a CTLA-4 antagonist selected from the group consisting of an anti-PD-1 antagonistic antibody, an anti-CTLA-4 antagonistic antibody and an immunoadhesin.

2. The combination according to claim 1, wherein the functionally equivalent variant of SEQ ID NO: 1 is selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO; 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, and SEQ ID NO: 10.

3. The combination according to any one of claims 1 or 2, wherein the chemical moiety that facilitates the cellular uptake of the polypeptide or the functionally equivalent variant thereof is a cell-penetrating peptide sequence and wherein said cell penetrating

peptide sequence and said polypeptide or functionally equivalent variant thereof form a fusion protein.

4. The combination according to claim 3, wherein the cell-penetrating peptide sequence is selected from the group consisting of GRKKRRQRRR (SEQ ID NO: 37) and RRRRRRLR (SEQ ID NO: 38).

5. The combination according to any one of claims 1 to 4, wherein the conjugate additionally comprises a further nuclear localization signal.

6. The combination according to any one of claims 1 to 5, with the proviso that the immuno-oncology agent is not a cytokine.

~~7. The combination according to any one of claims 1 to 6, wherein the immuno-oncology agent is an antagonist of a protein that inhibits T cell activation or an immune checkpoint inhibitor.~~

~~8. The combination according to claim 7, wherein the antagonist of a protein that inhibits T cell activation is selected from an anti-PD-1 and anti-CTLA-4.~~

~~9. The combination according to claim 8, wherein the antagonist of a protein that inhibits T cell activation is an anti-PD-1.~~

~~10~~7. The combination according to any one of claims 1~~8~~ to~~or~~ 6~~9~~, wherein the antagonist is an antagonistic antibody.

~~11~~8. The combination according to claim 7~~10~~, wherein the antagonistic antibody is pembrolizumab.

~~12~~9. The combination according to any one of claims 1 to 8~~11~~, wherein the first component is a polypeptide comprising the sequence SEQ ID NO: 1.

~~13~~10. A pharmaceutical composition comprising a pharmaceutically effective amount of a combination according to any one of claims 1 to 9~~12~~ and a pharmaceutically acceptable excipient.

~~14~~11. A combination according to any one of claims 1 to 9~~12~~ or a pharmaceutical composition according to claim 10~~3~~ for use in medicine.

~~15~~12. Use of a~~A~~ combination according to any one of claims 1 to 9~~12~~ or a pharmaceutical composition according to claim 10~~3~~ in~~for~~ the manufacture of a medicament for ~~use in~~ the ~~prevention and/or~~ treatment of cancer.

~~16~~13. The ~~combination or pharmaceutical composition for~~ use according to claim 12~~5~~, wherein the cancer is lung cancer.

~~17~~14. The ~~combination or pharmaceutical composition for~~ use according to any one of claims 11~~14~~ to 13~~16~~, wherein the composition is to be administered systemically or intranasally.

~~18~~15. The ~~combination or pharmaceutical composition for~~ use according to claim 14~~17~~, wherein the intranasal administration is to be performed by instillation or nasal inhalation.

~~19~~16. The ~~combination or pharmaceutical composition for~~ use according to any one of claims 11~~14~~ to 13~~16~~, wherein the first component is to be administered intranasally or intravenously and the second component is to be administered systemically.

~~20~~17. The ~~combination or pharmaceutical composition for~~ use according to any one of claims 11~~14~~ to 16~~19~~, wherein the polypeptide or the functionally equivalent variant thereof, or the conjugate, synergistically interacts with the immuno-oncology agent in treating cancer.