

DESCRIPTION

METHODS AND COMPOSITIONS FOR TUSC2 IMMUNOTHERAPY

[0001] This application claims the benefit of United States Provisional Patent Application No. 62/407,329, filed October 12, 2016, the entirety of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] The present embodiments provided herein relate generally to the fields of molecular biology, immunology and cancer therapy.

2. Description of Related Art

[0003] As the molecular and genetic mechanisms of oncogenesis become better elucidated, the focus of cancer therapy has shifted from the tissue to the genetic level (Bishop, 1991). Mutations in two major classes of genes, oncogenes and tumor suppressor genes (TSGs), play central roles in the oncogenic process. TSGs appear to require homozygous deletion or mutation for inactivation, and restoration of TSG expression is feasible in human tumors (Lowe *et al.*, 2004; Roth, 2006). Homozygous deletions in the 3p21.3 region in lung cancer cell lines and primary lung tumors have led to the identification of multiple genes with tumor suppressor activity from this region (Lerman *et al.*, 2000). These deletions have led to the development of targeted anti-cancer therapies. However, it remains unclear how the efficacy of such therapies could be enhanced.

SUMMARY

[0004] In one aspect, the present disclosure refers to the use of a TUSC2 ~~therapy-expression vector~~ in the manufacture of a first medicament and use of an anti-PD1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in for combination therapy of to treat a lung cancer in a subject, wherein the subject has been or is being treated with at least one immune checkpoint inhibitor. In another aspect, the present disclosure refers to the use of a TUSC2 expression vector in the manufacture of a medicament for use in combination therapy for treating lung cancer in a subject, wherein said medicament is to be administered in combination with an anti- PD1 antibody. In one example, there is disclosed the use of a TUSC2 therapeutic and an immune checkpoint inhibitor in the manufacture of a combination therapy for use in treating a lung cancer. In one example, there is described a method of treating a subject having a cancer comprising administering a tumor suppressor therapy (*e.g.*, a TUSC2 therapy) in conjunction with an immune checkpoint inhibitor. Thus, a method is disclosed for treating a subject having a cancer, wherein the subject is being treated with (or was previously administered) at least one immune checkpoint inhibitor, the method comprising administering a tumor suppressor therapy, such as a TUSC2 therapy, to the subject. For example, a subject to be treated with a TUSC2 therapy can be a subject who was administered an immune checkpoint inhibitor less that one hour, 6 hours, 12 hours, 1 day, 3 days, one week or two weeks before administration of the TUSC2 therapy. As used herein, a TUSC2 therapy can be any

CLAIMS

What Is Claimed Is:

1. Use of a TUSC2 ~~therapy-expression vector~~ in the manufacture of a first medicament and use of an anti-PD1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in ~~for combination therapy of~~ to treat lung cancer in a subject, wherein the subject has been or is being treated with at least one immune checkpoint inhibitor.
2. Use of a TUSC2 expression vector in the manufacture of a medicament for use in combination therapy for treating lung cancer in a subject, wherein said medicament is to be administered in combination with an anti- PD1 antibody.
2. ~~The use of claim 1, further comprising at least one immune checkpoint inhibitor to be administered to the subject.~~
3. The use of any one of claims 1 or 2, wherein the anti- PD1 antibody ~~at least one immune checkpoint inhibitor~~ is to be administered to the subject before the TUSC2 ~~therapy~~expression vector.
4. The use of any one of claims 1 or 2, wherein the anti- PD1 antibody ~~at least one immune checkpoint inhibitor~~ is to be administered to the subject after or concomitantly with the TUSC2 ~~therapy~~expression vector.
5. The use of any one of claims 1 or 2, wherein the subject had been administered the anti- PD1 antibody ~~at least one immune checkpoint inhibitor~~ no more than two weeks before the TUSC2 ~~therapy~~expression vector.
6. ~~The use of claim 1, wherein the at least one immune checkpoint inhibitor comprises an anti PD1 agent.~~
7. ~~The use of claim 6, wherein the anti PD1 agent comprises an anti PD1 antibody, anti-PDL1 antibody, or an anti PDL2 antibody.~~
8. ~~The use of claim 6, wherein the anti PD1 agent is nivolumab, pembrolizumab, pidilizumab, AMP 514, REGN2810, CT 011, BMS 936559, MPDL3280A or AMP 224.~~
9. ~~The use of claim 1, wherein the at least one immune checkpoint inhibitor is selected from an inhibitor of cytotoxic T lymphocyte associated protein 4 (CTLA-4), a human programmed cell death 1 (PD-1), programmed death ligand 1 (PD-L1), programmed~~

death ligand 2 (PD-L2), lymphocyte activation gene 3 (LAG-3), B and T lymphocyte attenuator (BTLA), B7 Homolog 3 (B7H3), B7 Homolog 4 (B7H4), T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), anti-killer cell immunoglobulin-like receptor (KIR), or adenosine A2A receptor (A2aR).

5

~~10.~~ The use of claim 1, wherein the at least one immune checkpoint inhibitor is an anti-CTLA-4 antibody.

10

~~11.~~ The use of claim 10, wherein the anti-CTLA-4 antibody is tremelimumab, or ipilimumab.

~~12.~~ The use of claim 1, wherein the at least one immune checkpoint inhibitor is an anti-killer cell immunoglobulin-like receptor (KIR) antibody.

15

~~13.~~ The use of claim 12, wherein the anti-KIR antibody is lirilumab.

~~14.6.~~ The use of any one of claims 1 or 2, wherein the subject has been or is to be treated with two immune checkpoint inhibitors.

20

~~15.7.~~ The use of claim ~~14~~6, wherein the two immune checkpoint inhibitors are an anti-PD1 antibody and an anti-CTL4 antibody.

25

~~16.~~ The use of claim 1, wherein the TUSC2 therapy comprises a TUSC2 expression vector to be administered.

~~17.8.~~ The use of any one of claims ~~16~~1 or 2, wherein the TUSC2 expression vector is plasmid DNA.

~~18.9.~~ The use of claim ~~17~~8, wherein the plasmid is pLJ143/KGB2/FUS1.

~~19.10.~~ The use of any one of claims 1 or 2~~16~~, wherein the TUSC2 expression vector is provided in a liposome.

30

~~20.11.~~ The use of claim ~~19~~10, wherein the liposome is a N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTAP):cholesterol liposome.

~~21.12.~~ The use of claim ~~20~~11, wherein the DOTAP:cholesterol ratio is between 1.5:1 and 1:1.5.

~~22.13.~~ The use of claim ~~20~~11, wherein the DOTAP:cholesterol ratio is about 10:9.

- 23.14. The use of claim ~~20~~11, wherein the TUSC2 expression vector and DOTAP:cholesterol liposome are to be administered in a dose of from 0.01 mg/kg to 0.10 mg/kg.
- 24.15. The use of any one of claims 1 or 2, wherein the TUSC2 ~~therapy expression vector~~ is to be administered two or more times.
- 5 25.16. The use of any one of claims 1 or 2, further comprising an anti-inflammatory agent to be administered.
- 26.17. The use of any one of claims 1 or 2, ~~wherein the TUSC2 therapy comprises further comprising~~ a TUSC2 polypeptide to be administered.
- 27.18. The use of claim ~~26~~17, wherein the TUSC2 polypeptide is myristoylated.
- 10 28.19. The use of claim ~~26~~17, wherein the TUSC2 polypeptide is comprised in a nanoparticle.
- 29.20. The use of claim ~~28~~19, wherein the nanoparticle is a lipid-based nanoparticle, a superparamagnetic nanoparticle, a nanoshell, a semiconductor nanocrystal, a quantum dot, a polymer-based nanoparticle, a silicon-based nanoparticle, a silica-based nanoparticle, a metal-based nanoparticle, a fullerene or a nanotube.
- 15 30.21. The use of any one of claims 1 or 2, further comprising a further anti-cancer therapy is to be administered to the subject.
- 31.22. The use of claim ~~30~~21, wherein the further anti-cancer therapy is chemotherapy, radiotherapy, gene therapy, surgery, hormonal therapy, anti-angiogenic therapy or cytokine therapy.
- 20 32.23. The use of claim ~~31~~22, wherein the further anti-cancer therapy is an EGFR inhibitor.
- 33.24. The use of any one of claims 1 or 2, wherein the lung cancer is a non-small cell lung cancer.
- 25 34.25. The use of any one of claims 1 or 2, wherein the cancer is a metastatic lung cancer.
- 35.26. The use of any one of claims 1 or 2, wherein the cancer is resistant to a least a first chemotherapy.
- 36.27. The use of claim ~~35~~26, wherein the cancer is resistant to a platinum-based chemotherapy.

~~37.28.~~ The use of any one of claims 1 or 2, wherein the TUSC2 ~~therapy-expression vector~~ and the anti- PD1 antibody ~~at least one immune checkpoint inhibitor~~ to be administered results in an increase of NK and/or CD8⁺ T cell density in the tumor.

5 ~~38.29.~~ The use of claim ~~3728~~, wherein the CD8⁺ T cell density increases by at least 3-fold.

~~39.30.~~ The use of any one of claims 1 or 2, wherein the TUSC2 ~~therapy-expression vector~~ and the anti- PD1 antibody ~~at least one immune checkpoint inhibitor~~ to be administered results in CcL3, CcL4, CcL21a, and/or CcL19 serum levels.

10

~~40.~~ Use of a TUSC2 therapeutic and an immune checkpoint inhibitor in the manufacture of a combination therapy for use in treating a lung cancer.

~~41.~~ The use of claims ~~40~~, wherein the immune checkpoint inhibitor is an anti-PD1 antibody.

~~42.31.~~ The use of claim ~~3223~~, wherein the EGFR inhibitor is a tyrosine kinase inhibitor.

15 ~~43.32.~~ The use of claim ~~3223~~, wherein the EGFR inhibitor is an EGFR binding antibody or aptamer.

~~44.33.~~ The use of claim ~~3223~~, wherein the EGFR inhibitor is gefitinib, erlotinib, cetuximab, matuzumab, panitumumab, AEE788; CI-1033, HKI-272, HKI-357 or EKB-569.

20