The need for therapy includes therapeutic compositions which combine cancer T-cell and immunotherapies with potent anti-cancer agents.

## BRIEF SUMMARY

**[0010]** This disclosure provides agents, compositions, and methods for use in treating or ameliorating the symptoms of cancer. The compositions can promote anti-tumor effects over a range of different cancers. Synergistic pharmaceutical therapies of this invention include use of potent, direct anti-tumor agents along with cancer immunotherapeutic agents. Cancer immunotherapeutic modalities of this disclosure include combination therapies with immune checkpoint inhibitor agents and protein immunotherapeutic agents. The agents, compositions, and methods of this invention may combine strategies for cancer immunotherapy with strategies for direct anti-tumor attack for treating various cancers.

**[0011]** In some examples, compositions and methods of this invention can increase efficacy, as well as reduce toxic side effects and adverse health effects in cancer treatment.

**[0012]** In further examples, methods and therapeutic strategies of this invention can include increased guidance for successful patient outcomes using appropriate biomarkers to select synergistic effects of the compositions.

**[0013]** Exemplary synergistic pharmaceutical therapies include a combination of active agents including an agent for inhibiting or suppressing expression of TGF-β2, an immune checkpoint inhibitor agent, and an interleukin immunotherapeutic agent.

**[0014]** In further examples, one or more biomarkers can be used to select subjects who benefit from the compositions and therapeutic methods, including IRF5 and ITGAM.

**[0015]** In certain examples, the compositions and therapeutic methods can be applied in combination with chemotherapy and other standard of care therapies for cancer.

**[0016]** In one aspect, the disclosure refers to a pharmaceutical composition comprising an agent for suppressing expression of TGF-β2 and a pharmaceutically acceptable carrier for treating or ameliorating the symptoms of a cancer in a subject, wherein the composition is to be administered in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic active agent.

**[0016a]** In another aspect, the disclosure refers to use of the composition as disclosed herein in

the preparation of a medicament for combination therapy to treat or ameliorate the symptoms of a cancer in a subject, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic active agent.

**[0016b]** In yet another aspect, the disclosure refers to a pharmaceutical combination comprising an agent for suppressing expression of TGF-β2 in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic active agent, and a pharmaceutically acceptable carrier for use in treating or ameliorating the symptoms of a cancer in a subject.

**[0016c]** Examples of this invention include the following:

**[0017]** A method for treating or ameliorating the symptoms of cancer in a subject in need, the method comprising: administering a composition comprising an agent for inhibiting or suppressing expression of TGF-β2; administering an immune checkpoint inhibitor; and administering an interleukin immunotherapeutic agent to the subject.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an agent for suppressing expression of TGF-β2 and a pharmaceutically acceptable carrier for treating or ameliorating the symptoms of a cancer in a subject, wherein the composition is to be administered in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic active agent.

2. The composition of claim 1, wherein the agent for suppressing expression of TGF-β2 is selected from Table 1 or Table 2, and chemically-modified variants thereof, LNA variants thereof, gapmer variants thereof, and any combination or pooling thereof.

3. The composition of claim 1 or 2, wherein the agent for suppressing expression of TGF-β2 is **CGGCATGTCTATTTTGTA** SEQ ID NO:1 or **C*G*G*C*A*T*G*T*C*T*A*T*T*T*T*G*T*A** SEQ ID NO:137.

4. The composition of any of claims 1-3, wherein the composition comprises a carrier of sterile water for injection, saline, isotonic saline, or a combination thereof.

5. The composition of any of claims 1-3, wherein the composition is substantially free of excipients.

6. The composition of any of claims 1-3, wherein the composition is stable for at least 14 days in carrier at 37°C.

7. The composition of any of claims 1-3, wherein the immune checkpoint inhibitor is an inhibitor of PD-1, CTLA-4, or PD-L1.

8. The composition of any of claims 1-3, wherein the immune checkpoint inhibitor is pembrolizumab, nivolumab, cemiplimab, spartalizumab, atezolizumab, avelumab, or durvalumab.

9. The composition of any of claims 1-3, wherein the interleukin immunotherapeutic active agent is a natural IL-2, a high dose IL-2, a recombinant IL-2, or aldesleukin.

10. Use of the composition of any of claims 1-9 in the preparation of a medicament for combination therapy to treat or ameliorate the symptoms of a cancer in a subject, wherein the medicament is to be administered in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic active agent.

11. The use of claim 10, wherein the cancer is a solid cancer, a pancreatic cancer, melanoma, lung cancer, breast cancer, multiple myeloma, or colorectal cancer.

12. The use of claim 10 or claim 11, wherein the medicament, the immune checkpoint inhibitor, and the interleukin immunotherapeutic active agent are to be administered concurrently, simultaneously, sequentially, or separately in time.

13. The use of any of claims 10-12, wherein the medicament is to be administered by infusion or injection.

14. The use of any of claims 10-12, wherein the subject after the administration has a reduced TGF-β2 expression.

15. The use of any of claims 10-12, wherein the subjects are to be selected using one or more biomarkers.

16. The use of claim 15, wherein the one or more biomarkers are a level of IRF5, a level of ITGAM, or a combination thereof.

17. The use of claim 15, wherein the one or more biomarkers is ITGAM and the subject is to be selected when expression of ITGAM is at a level above that found in a healthy patient.

18. The use of claim 15, wherein the subject after the administration has an increased level of IRF5.

19. The use of claim 15, wherein the subject after the administration has an increased level of ITGAM.

20. The use of claim 15, wherein the medicament is to be administered in combination with a therapeutically sufficient amount of a pharmaceutical composition comprising an expression product of IRF5 or ITGAM .

21. The use of claim 20, wherein the expression product is an mRNA, a polypeptide, a protein, or fragment thereof, or combination thereof.

22. The use of claim 15, wherein the administration increases a survival rate of the subject at month 6, 12, 18, 24, 30, or 36.

23. The use of claim 15, wherein the medicament is to be administered in combination with a standard of care treatment for cancer, wherein the standard of care treatment comprises chemotherapy or radiation therapy.

24. A pharmaceutical combination comprising an agent for suppressing expression of TGF-β2 in combination with an immune checkpoint inhibitor and an interleukin immunotherapeutic

active agent, and a pharmaceutically acceptable carrier for use in treating or ameliorating the symptoms of a cancer in a subject.