COMBINATION THERAPIES FOR THE TREATMENT OF CANCER

BACKGROUND

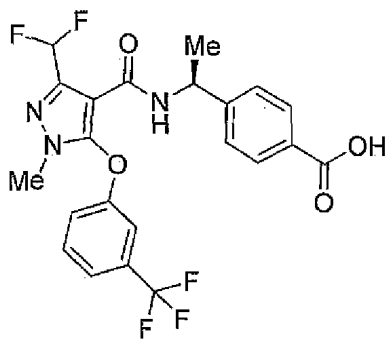
Blocking of prostaglandin E2 (PGE2) signaling through the interaction of PGE2 with the prostaglandin E receptor 4 (EP4) by antagonists has been shown to be effective in reducing inflammation (Chen et al. (2010) *British J. Pharmacol.* **160**, 292–310). PGE2 has also been implicated as an important constituent in the immunosuppressive environment created by many solid tumors (Whiteside (2010) *Expert Opinion in Biological Therapy.* 2010. **10**, 1019–1035), and inhibition of EP4 signaling by antagonists were shown to reduce tumor growth (Terada et al. (2010) *Cancer Res.* **70**, 1606–1615) and tumor metastasis in tumor animal models (Yang et al. (2006) *Cancer Res.* **66**, 9665–9672).

Even with the most advanced cancer therapies, there continues to be a medical need for more effective treatments for solid cancers, particularly cancer that has metastasized.

SUMMARY

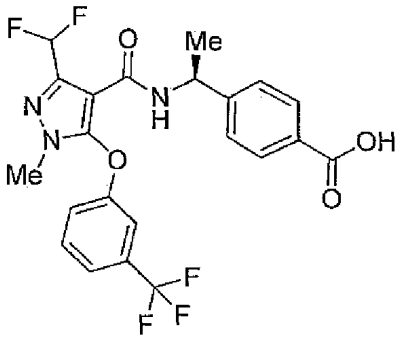
The anti-tumor activities of various combinations of an EP4 antagonist with: radiation; antibodies to cytotoxic t-lymphocyte antigen 4 (anti-CTLA4); antibodies to programmed death ligand 1 (anti-PDL1); antibodies to programmed cell death protein 1 (anti-PD1); and anti-metabolites have been examined. The results from this examination have indicated improved and/or synergistic anti-tumor activities by the combination of the EP4 antagonist with the other therapies as compared to single agent treatment alone, and in some embodiments this may result in a memory immune response against the tumor, even as against a different cancer.

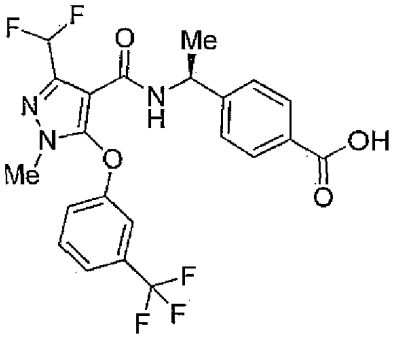
Thus, in one aspect of the invention, provided is the use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy, an antibody therapy, and combinations thereof; wherein the EP4 antagonist is:



or a pharmaceutically acceptable salt thereof. In

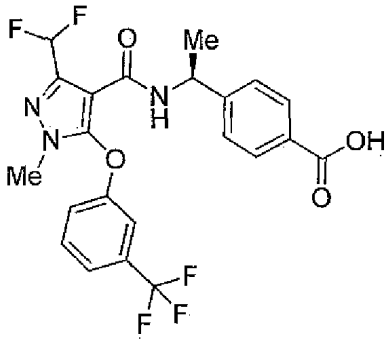
another aspect, the present invention refers to the use of an EP4 antagonist in the manufacture of a medicament for generating a memory immune response against a cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy, an antibody therapy, and combinations thereof;

wherein the EP4 antagonist is:  or a pharmaceutically acceptable salt thereof. In still another aspect, the present invention refers to the use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with an anti-metabolite chemotherapy, and wherein

the EP4 antagonist is:  or a pharmaceutically acceptable salt thereof.

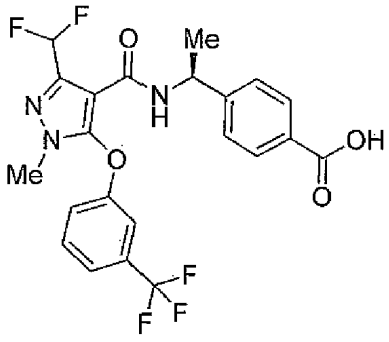
WHAT IS CLAIMED IS:

1. Use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy, an antibody therapy, and combinations thereof; wherein the EP4 antagonist is:



or a pharmaceutically acceptable salt thereof.

2. Use of an EP4 antagonist in the manufacture of a medicament for generating a memory immune response against a cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy, an antibody therapy, and combinations thereof; wherein the EP4 antagonist is:



or a pharmaceutically acceptable salt thereof.

3. The use of claim 1 or 2, wherein the therapy is radiation therapy.

4. The use of claim 1, wherein said treating comprises an abscopal effect.

5. The use of claim 2, wherein said generating the memory immune response comprises an abscopal effect.

6. The use of claim 1 or 2, wherein the therapy is antibody therapy.

7. The use of claim 6, wherein the antibody therapy is selected from the group consisting of: CTLA4 antibody therapy, PDL1 antibody therapy and PD1 antibody therapy.

8. The use of any of claims 1-7, wherein the cancer is selected from the group consisting of breast cancers, cervical cancers, colorectal cancers, endometrial cancers, glioblastomas, head and neck cancers, kidney cancers, liver cancers, lung cancers, medulloblastomas, ovarian cancers, pancreatic cancers prostate cancers, skin cancers (e.g., melanoma) and urinary tract cancers.

9. The use of any of claims 1–8, wherein the cancer is metastatic cancer.

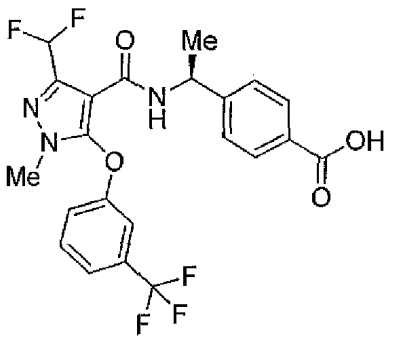
10. The use of any of claims 2–9, wherein the memory immune response comprises epitope spreading.

11. The use of any one of the preceding claims, wherein the use further comprises that an anti-metabolite chemotherapy is to be administered in combination with the EP4 antagonist and said therapy.

12. The use of claim 11, wherein the anti-metabolite is a deoxynucleoside analog.

13. The use of claim 12, wherein the deoxynucleoside analog is gemcitabine or capecitabine.

14. Use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with an anti-metabolite chemotherapy, and wherein the EP4 antagonist is:



or a pharmaceutically acceptable salt thereof.

15. The use of claim 14, wherein the anti-metabolite is a deoxynucleoside analog.

16. The use of claim 15, wherein the deoxynucleoside analog is gemcitabine.

17. The use of claim 15, wherein the deoxynucleoside analog is capecitabine.

18. The use of claim 14, wherein the anti-metabolite is fluorouracil.

19. The use of claim 11, wherein the anti-metabolite is fluorouracil.