METHODS OF TREATING CANCER AND OTHER CONDITIONS WITH A MU OPIOID RECEPTOR ANTAGONIST

RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application No. 63/318,465, filed on March 10, 2022, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0002] This disclosure relates to using Mu Opioid Receptor (MOR) antagonists, in particular axelopran, alone or in combination with an inhibitor of the PD-1/PD-L1 pathway, and/or an inhibitor of VEGF to treat angiogenesis and cancer.

BACKGROUND

[0003] Mu Opioid Receptor (MOR) antagonists are commonly used to treat opioid dependence and alcohol dependence. They are also used treat the side effects associated with treatment of mu opioid agonists such as *e.g.* morphine. Some of these side effects include induced bowel dysfunction, for example in cancer patients and in postoperative ileus.

[0004] In addition, MOR antagonists show other promising uses. For example, according to the Abstract, WO 2016061531 discloses "methods for preventing or treating tumor growth, tumor metastasis and/or abnormal proliferation of tumor cells in a subject, wherein the methods involve administration of a pharmaceutical composition comprising methylnaltrexone." Due to their widespread use and relatively high tolerance in patients, in particular when compared to conventional chemotherapy, in view of WO 2016061531, MOR antagonists present an attractive target for treating cancer.

[0005] What is needed are additional treatments for angiogenesis and cancer.

SUMMARY

[0006] This disclosure relates to use of Mu Opioid Receptor (MOR) antagonists, in particular axelopran, alone or in combination with an inhibitor of the PD-1/PD-L1 pathway, and/or an inhibitor of VEGF to treat angiogenesis and cancer.

[0007] The disclosure is directed to reducing or inhibiting angiogenesis via the use of a MOR antagonist (such as *e.g.* axelopran). The disclosure is directed to a method of reducing or inhibiting endothelial cell growth comprising contacting an endothelial cell with a MOR antagonist. The disclosure is directed to a method of

reducing angiogenesis in a patient in need thereof comprising administering a MOR antagonist to the patient. The disclosure is directed to a method of reducing angiogenesis in a cancer patient comprising administering a MOR antagonist to the cancer patient.

[0008] The disclosure is directed to using MOR antagonists to treat cancer or to treat specific aspects of cancer. Accordingly, the disclosure is directed to a method of reducing tumor growth in a cancer patient by administering a MOR antagonist to the cancer patient. The disclosure is directed to a method of reducing metastasis in a cancer patient by administering a MOR antagonist to the cancer patient.

[0009] The disclosure is directed to a method of improving the immune response to a tumor comprising administering a MOR antagonist to a cancer patient. In certain examples, the method increases infiltration of immune cells, such as *e.g.* NK cells, lymphocytes and/or monocytes/macrophages, into the tumor. For example, the method increases infiltration of $CD3^+$, $CD244^+$, and MMD^+ immune cells.

[0010] The disclosure is directed to a method of treating cancer by administering axelopran, naloxegol, or combinations thereof to a cancer patient. In one example, the method reduces angiogenesis, tumor growth, and/or metastasis. Alternatively, the method inhibits angiogenesis, tumor growth, and/or metastasis. In some examples, the cancer is a melanoma, colon, pancreatic, or breast cancer.

[0011] The disclosure also provides for combination therapy using MOR antagonist in combination with a checkpoint inhibitor and/or an inhibitor of VEGF.

[0011a] In one aspect, the present disclosure provides use of a MOR antagonist and a checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer.

[0011b] In another aspect, the present disclosure provides use of an MOR antagonist in the manufacture of a medicament for use in combination with a checkpoint inhibitor for the treatment of cancer.

[0012] The disclosure is directed to a method of treating cancer comprising administering a MOR antagonist and a checkpoint inhibitor and/or an inhibitor of VEGF to a cancer patient. Where mentioned above, the MOR antagonist and the checkpoint inhibitor and/or the inhibitor of VEGF synergistically treat the cancer.

[0013] The disclosure is directed to a method of improving the immune response to a tumor comprising administering a MOR antagonist and a checkpoint inhibitor and/or an inhibitor of VEGF to a cancer patient. In certain examples, the method increases infiltration of immune cells (such as NK cells, lymphocytes, and/or monocytes/macrophages) into the tumor. In a specific example, the method increases infiltration of CD3+, CD244+, and MMD+ immune cells. In examples of the method, the MOR antagonist and the checkpoint inhibitor synergistically improve the immune response to the tumor.

[0014] In some examples, the methods and combination therapies of the disclosure are particularly useful for treating patients that are not receiving opioid treatment. In other examples, the methods and combination therapies of the disclosure are particularly useful for treating patients that are receiving opioid treatment.

[0015] In certain examples of the methods and combination therapies, the MOR antagonist comprises axelopran, naloxegol, methylnaltrexone, or combinations thereof. In specific preferred examples, the MOR antagonist is axelopran. In some examples, the MOR antagonist does not comprise (*i.e.* excludes) methylnaltrexone, naltrexone, and/or naloxone.

[0016] In some examples of the combination therapies, the checkpoint inhibitor is an inhibitor of the PD-1/PD-L1 pathway. For example, the inhibitor of the PD-1/PD-L1 pathway is an antibody, such as *e.g.* an antibody that binds to PD-1. In some examples, the antibody is a humanized antibody, such as *e.g.* pembrolizumab.

[0017] In other examples of combination therapy, the inhibitor of VEGF is an anti-VEGF antibody, such as an anti-VEGF-A antibody. In one example, anti-VEGF antibody is humanized. In certain examples, the inhibitor of VEGF is bevacizumab. In specific examples of the combination therapy, the inhibitor of VEGF is intravenously injected.

[0018] In the methods or combination therapy, a variety of administration routes are used. In one example, the methods or combination therapy include orally or subcutaneously administering the MOR antagonist.

[0019] The methods and combination therapy of the disclosure including administering pharmaceutical composition containing the MOR antagonist and a pharmaceutically acceptable carrier. In one example, such a composition is formulated for modified release.

[0020] When used in combination therapy, the checkpoint inhibitor is administered concurrently, before, or after the MOR antagonist. Similarly, the VEGF antagonist is administered concurrently, before, or after the MOR antagonist. Furthermore, the inhibitor of VEGF is administered concurrently, before, or after the inhibitor of the PD-1/PD-L1 pathway.

[0021] The disclosure is directed to a method of reducing tumor size comprising contacting a tumor with axelopran, naloxegol, or combinations thereof. The disclosure also relates to kits containing a MOR antagonist (*e.g.* axelopran) a checkpoint inhibitor and/or an inhibitor of VEGF.

[0022] Other features and advantages of the disclosure will be apparent from the detailed description and examples that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] For the purpose of illustrating the invention, there are depicted in the drawings certain embodiments of the invention. However, the invention is not limited to the precise arrangements and instrumentalities of the embodiments depicted in the drawings.

[0024] FIG. 1A and FIG. 1B show HUVEC cell tube formation in the presence of increasing MOR antagonist concentrations (0-1000 nM). Axelopran is compared to naloxegol and methylnaltrexone (MNTX).

[0025] FIG. 2A and 2B show blood vessel formation in the presence of increasing MOR antagonist (axelopran) concentrations (0, 0.1, 0.5, 1.0 mg/kg) in the chicken CAM assay in comparison to docetaxel. FIG. 2A shows a picture of CAM Angiogenesis. FIG. 2B panels A) to D) show graphs testing the impact of axelopran, bevacizumab and axelopran + bevacizumab on CAM angiogenesis.

[0026] FIG. 3A to 3C show schematic summaries of the three model systems used to assess the contribution of endogenous MOR activity on tumor progression. FIG. 3A shows a schematic summary of the melanoma model system. FIG. 3B shows a schematic summary of the breast cancer model system. FIG. 3C shows a schematic summary of the colon cancer model system.

[0027] FIG. 4A to FIG. 4C show Zebra fish larvae survival up to 72 hours in the presence of increasing axelopran concentration in the incubation water. FIG. 4A and FIG. 4B show graphs measuring the percentage survival as a function of time. FIG. 4C shows pictures of Zebra fish larvae at 24 hours, 48 hours, and 72 hours of exposure to vehicle, 100 μM axelopran, and 500 μM axelopran. Doses up the 100 μM allowed survival and development of pathological lesions at levels no different that the vehicle control.

[0028] FIG. 5 shows a schematic of time course of Zebra fish larvae development.

[0029] FIG. 6A and FIG. 6B show representative displays of melanoma tumor growth size (y-axis) (normalized as % of vehicle control) vs number of metastasis (x-axis) in zebra fish treated with 10 μM axelopran (n=18) (FIG. 6A) or vehicle control (n=32) (FIG. 6B).

[0030] FIG. 7 shows a summary of melanoma tumor progression (tumor size x # metastasis) in the presence of increasing axelopran concentrations or the checkpoint inhibitor pembrolizumab. For experiments using pembrolizumab, exogenous tumor-infiltrating

CLAIMS

What is claimed:

1. Use of a MOR antagonist and a checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer.

2. The use of claim 1, wherein the use improves an immune response to a tumor.

3. The use of claim 2, wherein the use increases infiltration of NK cells, lymphocytes and/or monocytes/macrophages into the tumor.

4. The use of claim 2, wherein the use increases infiltration of $CD3^+$, $CD244^+$, and MMD^+ immune cells into the tumor.

5. The use of claim 2, wherein the use synergistically improves the immune response to the tumor.

6. The use of claim 1, wherein the MOR antagonist comprises axelopran, naloxegol, methylnaltrexone, or combinations thereof.

7. The use of claim 6, wherein the MOR antagonist is axelopran.

8. The use of claim 1, wherein the checkpoint inhibitor is an inhibitor of the PD-1/PD-L1 pathway.

9. The use of claim 8, wherein the inhibitor of the PD-1/PD-L1 pathway is an antibody.

10. The use of claim 9, wherein the antibody is an antibody that binds to PD-1.

11. The use of claim 10, wherein the antibody that binds to PD-1 is a humanized antibody.

12. The use of claim 11, wherein the humanized antibody is pembrolizumab.

13. The use of claim 1, wherein the medicament further comprises an inhibitor of VEGF.

14. The use of claim 1, wherein the inhibitor of VEGF is an anti-VEGF antibody.

15. Use of an MOR antagonist in the manufacture of a medicament for use in combination with a checkpoint inhibitor for the treatment of cancer.

16. The use of any one of claims 1-15, wherein the cancer is melanoma, pancreatic cancer, colon cancer, or breast cancer.

17. The use of claim 16, wherein the cancer is melanoma.

18. The use of claim 16, wherein the cancer is pancreatic cancer.

19. The use of claim 16, wherein the cancer is colon cancer.

20. The use of claim 16, wherein the cancer is breast cancer.

21. The use of claim 16, wherein the use synergistically improves one or more symptoms of the cancer, and/or synergistically decreases a tumor volume of the cancer.