Target for anti-cancer therapy

This invention relates to the identification of RNR as a target for therapeutic formulations for increasing the efficacy of immune checkpoint regulators in the treatment of certain cancers.

BACKGROUND OF THE INVENTION

Immune checkpoint regulators (ICR) show enormous promise in the treatment of cancer. However, to date, the benefits of ICR treatment is generally limited to those tumours having inherent genomic instability such as Microsatellite Instable (MSI) tumours, representing less than 5% of tumours. There is therefore a need to find new mechanisms for improving ICR response in those tumours that do not naturally show genomic instability.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a composition in the manufacture of a medicament for stimulating neoantigen production in a cancerous tumour in a subject, wherein the use is for improving the subject's immune response against the cancerous tumour, and wherein the composition comprises a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase.

In another aspect of the present disclosure, there is provided a use of a composition comprising a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase, in the manufacture of a medicament for improving the immune response to a cancerous tumour in a subject in need thereof, wherein:

a. the level of neoantigen presentation of the cancerous tumour is assessed;

b. the level of neoantigen presentation is determined to be below a threshold to induce an immune response, and

c. if the level of neoantigen presentation is below a threshold to induce an immune response, the medicament is to be administered to the subject.

The present disclosure relates to the identification of ribonucleotide reductase (RNR), and its component genes or their protein products, as a target whose inactivation or modulation leads to an increase in mutational rates, as assessed, for example, by a frameshift reporter assay. Stimulating an increase in the mutational rate in a

tumour leads to an increase in neoantigen expression. Thus RNR is a target for the treatment of cancer. In particular, inactivators or modulators of RNR may make cancer cells more susceptible to immunotherapy.

Accordingly, in a first example, the present disclosure provides a composition for use in stimulating neoantigen production in a cancerous tumour in a subject, wherein the composition is for improving the subject's immune response against the cancerous tumour, and wherein the composition comprises a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase (RNR).

In one example, the compound is a negative modulator which causes frameshift mutations as measured by a frameshift reporter assay. Suitably, the frameshift reporter assay measures a change in luminescence through a reporter assay as described herein wherein the compound for use in accordance with the present disclosure negatively modulates the expression, function or stability of RNR and results in a mean luminescence greater than 3 standard deviations from a control in a frameshift reporter assay as described herein, or wherein inhibition results in a mean luminescence which is more than a 150% increase compared to a control.

In one example, the composition in accordance with the present disclosure comprises a compound having a therapeutic concentration range wherein frameshift mutations increase at a greater rate than cell viability decreases. Suitably frameshift mutations are measured by a frameshift reporter assay, while cell viability is measured using a standard cell viability assay. In another example, the compound has a K_i (RNR) equal to or below its $GI_{50.}$ Suitably, K_i (RNR) may be measured by application of the Michaelis-Menten model; GI_{50} may be measured in standard assays such as the assay described herein, for example.

In another example, there is provided a composition in accordance with the present disclosure which is capable of delivering a concentration of compound to the cancerous tumour, wherein the concentration of compound is within the therapeutic concentration range. Suitably the composition comprises a compound at a suitable concentration range to increase frameshift mutations at a greater rate than decreasing cell viability and thereby have a therapeutic effect.

In one example, the composition in accordance with the present disclosure comprises a compound which is an inhibitor of ribonucleotide reductase. Suitably, such a compound may be a polypeptide, a polynucleotide, an antibody, an aptamer, a peptide, a small molecule, an RNA-based drug, such as siRNA or RNAi, a genetic construct for targeted gene editing, or any other suitable chemical.

Suitably, the composition in accordance with the present disclosure comprises a small molecule inhibitor of RNR, such as any of clofarabine, triapine, cytarabine, cladribine, azathioprine, fludarabine, 5-flurouracil, hydroxyurea, motexafin gadolinium, gallium maltolate and gallium nitrate, or a pharmaceutically acceptable salt thereof. In one example, the composition in accordance with the present disclosure comprises a compound selected from cladribine, clofarabine, triapine, cytarabine and fludarabine, or a pharmaceutically acceptable salt thereof.

In one example of the present disclosure, the cancerous tumour is microsatellite stable. In other examples, the cancerous tumour is one which is otherwise unlikely to be responsive to treatment with immune checkpoint regulators (ICR). Suitably such cancerous tumours may be characterised by a low mutator phenotype.

In one example, the cancerous tumour is selected from neuroblastoma, glioma, glioblastoma, prostate, ovary, myeloma, pancreas, breast, papillary kidney, B cell lymphoma, clear cell kidney, head and neck, liver, cervix, uterus, bladder, colorectal, small cell lung, espohagus, stomach, non-small cell lung cancer, and melanoma.

In one example there is provided a composition in accordance with the present disclosure wherein the treatment comprises administering a therapeutically effective amount of the compound to the subject.

In another example, there is provided a composition in accordance with the present disclosure for use in combination with an immunotherapy, suitably an immune checkpoint inhibitor or a combination of immune checkpoint inhibitors. An immune checkpoint inhibitor may be selected from PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor. Suitable immune checkpoint inhibitors include pembrolizumab, nivolumab, ipilimumab, atezolizumab, avelumab, durvalumab, tremelimumab, tislelizumab, pidilizumab, AMP-224, AMP-514, PDR001, BMS-936559.

In one example, the immunotherapy is administered subsequent to or concurrent with the composition in accordance with the present disclosure.

In another example, the present disclosure provides a method for improving the immune response to a cancerous tumour in a subject in need thereof, the method comprising the steps of:

a. assessing the level of neoantigen presentation of the cancerous tumour;
b. determining whether the level of neoantigen presentation is below a threshold to induce an immune response, and
c. if the level of neoantigen presentation is below a threshold to induce an immune response, administering a composition comprising a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase.

In one example, the level of neoantigen presentation is assessed with reference to the number of mutations in the genome of the cancerous tumour. In some examples, the threshold to induce an immune response may be assessed as a significant increase in mutations over baseline. This may vary depending on tumour type. Suitably, the threshold to induce an immune response is approximately 90 to 150 mutations per megabase, preferably 100 mutations per megabase.

In one example, the method in accordance with the present disclosure comprises the further steps of:

d. reassessing the level of neoantigen presentation of the cancerous tumour; and/or
e. Administering an immunotherapy to the subject.

Suitably, the composition for administration is a composition in accordance with any example of the present disclosure.

CLAIMS

1. Use of a composition in the manufacture of a medicament for stimulating neoantigen production in a cancerous tumour in a subject, wherein the use is for improving the subject's immune response against the cancerous tumour, and wherein the composition comprises a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase.

1. The use as claimed in claim 1 wherein the compound causes frameshift mutations as measured by a frameshift reporter assay.

2. The use as claimed in claim 1 wherein the compound results in a mean luminescence greater than 3 standard deviations from a control in a frameshift reporter assay as described herein, or wherein inhibition results in a mean luminescence which is more than a 150% increase compared to a control.

3. The use as claimed in claim 1, 2 or 3 wherein the compound has a therapeutic concentration range wherein frameshift mutations increase at a greater rate than cell viability decreases as measured by a frameshift reporter assay.

4. The use as claimed in claim 4 which is capable of delivering a concentration of compound to the cancerous tumour, wherein the concentration of compound is within the therapeutic concentration range.

5. The use as claimed in any preceding claim wherein the compound is an inhibitor of ribonucleotide reductase.

6. The use as claimed in any preceding claim wherein the compound is a polypeptide, polynucleotide, antibody, aptamer, peptide, small molecule, an RNA-based drug, a genetic construct for targeted gene editing, or any other suitable chemical.

7. The use as claimed in any preceding claim wherein the compound is a small molecule.

8. The use as claimed in claim 8 wherein the compound is selected from clofarabine, triapine, cytarabine, cladribine, azathioprine, fludarabine, 5-flurouracil, hydroxyurea, motexafin gadolinium, gallium maltolate and gallium nitrate, or a pharmaceutically acceptable salt thereof.

9. The use as claimed in claim 9 wherein said compound is selected from cladribine, clofarabine, cytarabine and fludarabine, or a pharmaceutically acceptable salt thereof.

10. The use as claimed in any preceding claim wherein the cancerous tumour is microsatellite stable.

11. The use as claimed in any preceding claim wherein the cancerous tumour is selected from neuroblastoma, glioma, glioblastoma, prostate, ovary, myeloma, pancreas, breast, papillary kidney, B cell lymphoma, clear cell kidney, head and neck, liver, cervix, uterus, bladder, colorectal, small cell lung, oesophagus, stomach, non-small cell lung cancer, and melanoma.

12. The use as claimed in claim 12 wherein the cancerous tumour is selected from head and neck, liver, cervix, uterus, bladder, colorectal, small cell lung, oesophagus, stomach, non-small cell lung cancer, and melanoma.

13. The use as claimed in claim 13 wherein the cancerous tumour is selected from head and neck, liver, cervix, uterus, bladder, colorectal, small cell lung, oesophagus, and stomach.

14. The use as claimed in any preceding claim wherein a therapeutically effective amount of the compound is to be administered to the subject.

15. The use as claimed in any preceding claim, wherein the composition is to be administered in combination with an immunotherapy.

16. The use as claimed in claim 15 wherein the immunotherapy is an immune checkpoint inhibitor or a combination of immune checkpoint inhibitors.

17. The use as claimed in claim 15 or 16 wherein the immunotherapy comprises an immune checkpoint inhibitor selected from PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor.

18. The use as claimed in claims 15 to 17 wherein the immunotherapy comprises an immune checkpoint inhibitor selected from pembrolizumab, nivolumab, ipilimumab, atezolizumab, avelumab, durvalumab, tremelimumab, tislelizumab, pidilizumab, AMP-224, AMP-514, PDR001, BMS-936559.

19. The use as claimed in any one of claims 15 to 18 wherein the immunotherapy is to be administered subsequent to or concurrent with the composition.

20. Use of a composition comprising a compound or a pharmaceutically acceptable salt thereof, which is a negative modulator of the expression, function or stability of ribonucleotide reductase, in the manufacture of a medicament for improving the immune response to a cancerous tumour in a subject in need thereof, wherein:
    a. the level of neoantigen presentation of the cancerous tumour is assessed;

    b. the level of neoantigen presentation is determined to be below a threshold to induce an immune response, and

    c. If the level of neoantigen presentation is below a threshold to induce an immune response, the medicament is to be administered to the subject.

21. The use as claimed in claim 21 wherein the level of neoantigen presentation is assessed with reference to the number of mutations in the genome of the cancerous tumour.

22. The use as claimed in claim 22 wherein the threshold to induce an immune response is 100 mutations per megabase.

23. The use as claimed in claim 21 to 23 comprising the further step of:
    d. Reassessing the level of neoantigen presentation of the cancerous tumour.

24. The use as claimed in claim 21 to 24 comprising a further step (e), wherein:
    e. an immunotherapy is to be further administered to the subject.

25. The use of any one of claims 21 to 25 wherein the composition is as claimed in any one of claims 1 to 20.