THERAPEUTIC RNA FOR OVARIAN CANCER

This disclosure relates to the field of therapeutic RNA to treat ovarian cancer. Ovarian cancer refers to any cancerous growth that begins in the ovary. It is the fifth most common cause of cancer deaths in women and the tenth most common cancer among women in the United States. Among the gynecologic cancers - those affecting the uterus, cervix, and ovaries - ovarian cancer has the highest rate of deaths.

Disclosed herein are compositions, uses, and methods for treatment of ovarian cancers. Administration of therapeutic RNAs to a patient having ovarian cancer disclosed herein can reduce tumor size, prolong time to progressive disease, and/or protect against metastasis and/or recurrence of the tumor and ultimately extend survival time.

Summary

In one aspect, the present disclosure provides for a composition or medical preparation comprising at least one RNA, wherein the at least one RNA encodes the following amino acid sequences: (i) an amino acid sequence comprising claudin 6 (CLDN6), or an immunogenic fragment of the CLDN6; (ii) an amino acid sequence comprising p53, or an immunogenic fragment of the p53; and (iii) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), or an immunogenic fragment of the PRAME, wherein the immunogenic fragment is immunologically equivalent to CLDN6, p53 or PRAME, respectively. In one example, provided herein is a composition or medical preparation comprising at least one RNA, wherein the at least one RNA encodes the following amino acid sequences:
(i) an amino acid sequence comprising claudin 6 (CLDN6), an immunogenic variant thereof, or an immunogenic fragment of the CLDN6 or the immunogenic variant thereof;
(ii) an amino acid sequence comprising p53, an immunogenic variant thereof, or an immunogenic fragment of the p53 or the immunogenic variant thereof; and
(iii) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), an immunogenic variant thereof, or an immunogenic fragment of the PRAME or the immunogenic variant thereof.

In one example, each of the amino acid sequences under (i), (ii), or (iii) is encoded by a separate RNA.

In one example, the composition or medical preparation is a pharmaceutical composition. In one example, the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

In one example, the composition or medical preparation is a kit. In one example, the RNAs and optionally the liposomes are in separate vials.

In one example, the composition or medical preparation further comprises instructions for use of the RNAs and optionally the liposomes for treating or preventing ovarian cancer.

In another aspect, the present disclosure provides the composition or medical preparation as described herein for use in therapy. In one example, provided herein is the composition or medical preparation described herein for pharmaceutical use. In yet another aspect, the present disclosure provides for a use of the composition or medical preparation as disclosed herein in the manufacture of a medicament for the therapeutic treatment of ovarian cancer. In one example, the present disclosure provides a use of the composition or medical preparation as described herein in the manufacture of a medicament for the therapeutic or prophylactic treatment of ovarian cancer. In one example, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder. In one example, the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing ovarian cancer. In one example, the composition or medical preparation described herein is for administration to a human.

In one example, the therapeutic or prophylactic treatment of a disease or disorder further comprises administering a further therapy. In one example, the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) radiotherapy, and (iii) chemotherapy. In one example, the further therapy comprises administering a further therapeutic agent. In one example, the further therapeutic agent comprises an anti-cancer therapeutic agent. In one example, the further therapeutic agent is

Claims

1. A composition or medical preparation comprising at least one RNA, wherein the at least one RNA encodes the following amino acid sequences:
(i) an amino acid sequence comprising claudin 6 (CLDN6), or an immunogenic fragment of the CLDN6;
(ii) an amino acid sequence comprising p53, or an immunogenic fragment of the p53; and
(iii) an amino acid sequence comprising Preferentially Expressed Antigen In Melanoma (PRAME), or an immunogenic fragment of the PRAME,
wherein the immunogenic fragment is immunologically equivalent to CLDN6, p53 or PRAME, respectively.

2. The composition or medical preparation of claim 1, wherein each of the amino acid sequences under (i), (ii), or (iii) is encoded by a separate RNA.

3. The composition or medical preparation of claim 1 or 2, wherein
(a) the RNA encoding the amino acid sequence comprising CLDN6 comprises the nucleotide sequence of SEQ ID NO: 2 or 3, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 2 or 3; and/or
(b) the amino acid sequence comprising CLDN6 comprises the amino acid sequence of SEQ ID NO: 1, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 1 and/or
(c) the RNA encoding the amino acid sequence comprising p53 comprises the nucleotide sequence of SEQ ID NO: 6 or 7, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 6 or 7; and/or
(d) the amino acid sequence comprising p53 comprises the amino acid sequence of SEQ ID NO: 5, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 5; and/or
(e) the RNA encoding the amino acid sequence comprising PRAME comprises the nucleotide sequence of SEQ ID NO: 10 or 11, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 10 or 11; and/or

(f) the amino acid sequence comprising PRAME comprises the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 9.

4. The composition or medical preparation of any one of claims 1 to 3, wherein the composition further comprises RNA encoding:
(iv) an amino acid sequence which breaks immunological tolerance, wherein the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 13, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 13.

5. The composition or medical preparation of claim 4, wherein the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 14 or 15, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 14 or 15.

6. The composition or medical preparation of any one of claims 1 to 5, wherein at least one of the amino acid sequences under (i), (ii), or (iii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence, or wherein each of the amino acid sequences under (i), (ii), or (iii) is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

7. The composition or medical preparation of any one of claims 1 to 6, wherein at least one RNA comprises the 5' cap $m_2^{7,2'-O}Gpp_sp(5')G$, or wherein each RNA comprises the 5' cap $m_2^{7,2'-O}Gpp_sp(5')G$.

8. The composition or medical preparation of any one of claims 1 to 7, wherein at least one RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 16, or a nucleotide

sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 16, or wherein each RNA comprises a 5' UTR comprising the nucleotide sequence of SEQ ID NO: 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 16.

9. The composition or medical preparation of any one of claims 1 to 8, wherein at least one amino acid sequence under (i), (ii), or (iii) comprises an amino acid sequence enhancing antigen processing and/or presentation, or wherein each amino acid sequence under (i), (ii), or (iii) comprises an amino acid sequence enhancing antigen processing and/or presentation, wherein the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 19, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 19.

10. The composition or medical preparation of claim 9, wherein the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 20.

11. The composition or medical preparation of any one of claims 1 to 10, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 21, or wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 21.

12. The composition or medical preparation of any one of claims 1 to 11, wherein at least one RNA comprises a poly-A sequence, or wherein each RNA comprises a poly-A sequence.

13. The composition or medical preparation of claim 12, wherein the poly-A sequence comprises at least 100 nucleotides.

14. The composition or medical preparation of claim 12 or 13, wherein the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 22.

15. The composition or medical preparation of any one of claims 1 to 14, (a) wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof, or (b) wherein the RNA is formulated for injection, or (c) wherein the RNA is formulated for intravenous administration.

16. The composition or medical preparation of any one of claims 1 to 15, wherein the RNA is formulated or is to be formulated as lipoplex particles, preferably wherein the RNA lipoplex particles are obtainable by mixing the RNA with liposomes.

17. The composition or medical preparation of claim 16, wherein at least one RNA encoding an amino acid sequence under (i), (ii), and/or (iii) is co-formulated or is to be co-formulated as lipoplex particles with the RNA encoding an amino acid sequence which breaks immunological tolerance, or wherein each RNA encoding an amino acid sequence under (i), (ii), and/or (iii) is co-formulated or is to be co-formulated as lipoplex particles with the RNA encoding an amino acid sequence which breaks immunological tolerance,
wherein the RNA encoding an amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 13, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the amino acid sequence of SEQ ID NO: 13.

18. The composition of any one of claims 1 to 17, which is a pharmaceutical composition, optionally wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

19. The medical preparation of any one of claims 1 to 17, wherein the medical preparation is a kit, optionally wherein the RNAs and optionally the liposomes are in separate vials.

20. The medical preparation of claim 19, further comprising instructions for use of the RNAs and optionally the liposomes for treating ovarian cancer.

21. The composition or medical preparation of any one of claims 1 to 20 for use in therapy.

22. Use of the composition or medical preparation of any one of claims 1 to 21 in the manufacture of a medicament for the therapeutic treatment of ovarian cancer.

23. The use of claim 22, wherein the therapeutic treatment further comprises that a further therapy is to be administered.

24. The use of claim 23, wherein the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) radiotherapy, and (iii) chemotherapy.

25. The use of claim 23 or 24, wherein the further therapy comprises that a further therapeutic agent is to be administered.

26. The use of claim 25, wherein the further therapeutic agent comprises an anti-cancer therapeutic agent.

27. The use of claim 25 or 26, wherein the further therapeutic agent is an anti-PD1 antibody, an anti-CTLA-4 antibody, or a combination of an anti-PD1 antibody and an anti-CTLA-4 antibody.