THERAPEUTIC RNA FOR PROSTATE CANCER

This disclosure relates to the field of therapeutic RNA to treat prostate cancer. Prostate cancer is a serious disease that affects thousands of men each year who are middle-aged or older. About 60 percent of the cases occur in men older than age 65. The American Cancer Society (ACS) estimates that 174,650 American men will be newly diagnosed with this condition in 2019. According to the Urology Care Foundation, prostate cancer is the second-leading cause of cancer deaths for men in the United States.

Disclosed herein are compositions, uses, and methods for treatment of prostate cancers. Administration of therapeutic RNAs to a patient having prostate 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 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 Kallikrein-2 (KLK2), an immunogenic variant thereof, or an immunogenic fragment of the KLK2 or the immunogenic variant thereof;
(ii) an amino acid sequence comprising Prostate Specific Antigen (PSA), an immunogenic variant thereof, or an immunogenic fragment of the PSA or the immunogenic variant thereof;
(iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP), an immunogenic variant thereof, or an immunogenic fragment of the PAP or the immunogenic variant thereof;

(iv) an amino acid sequence comprising Homeobox B13 (HOXB13), an immunogenic variant thereof, or an immunogenic fragment of the HOXB13 or the immunogenic variant thereof; and

(v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1), an immunogenic variant thereof, or an immunogenic fragment of the NKX3-1 or the immunogenic variant thereof.

In one aspect, provided herein is a composition or medical preparation comprising RNA, wherein the RNA encodes the following amino acid sequences: (i) an amino acid sequence comprising Kallikrein-2 (KLK2); (ii) an amino acid sequence comprising Prostate Specific Antigen (PSA); (iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP); (iv) an amino acid sequence comprising Homeobox B13 (HOXB13); and (v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1), wherein each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) is encoded by a separate RNA, and each RNA comprises a 5'-cap, a 5'-UTR, a 3'-UTR and a poly-A sequence, wherein the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 2; the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 6; the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 10; the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 14, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 14; and the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 18, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 18.

In another aspect, the present disclosure provides the composition or medical preparation as described herein for use as a pharmaceutical. In yet another aspect, the present disclosure provides a use of the composition or medical preparation as described herein in the manufacture of a medicament for treating or preventing prostate cancer.

In a further aspect, the present disclosure provides a use of RNA in the manufacture of a medicament for treating prostate cancer in a subject, wherein the RNA encodes the following amino acid sequences:

(i) an amino acid sequence comprising Kallikrein-2 (KLK2);

(ii) an amino acid sequence comprising Prostate Specific Antigen (PSA);

(iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP);

(iv) an amino acid sequence comprising Homeobox B13 (HOXB13); and

(v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1).

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

In one example,

(i) the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 3 or 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 3 or 4; and/or

(ii) the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 1 or 2, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 2.

In one example,

(i) the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 7 or 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 7 or 8; and/or

(ii) the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 5 or 6, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 5 or 6.

In one example,

(i) the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 11 or 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11 or 12; and/or

(ii) the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 9 or 10.

In one example,

(i) the RNA encoding the amino acid sequence under (iv) comprises the nucleotide sequence of SEQ ID NO: 15 or 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 15 or 16; and/or

(ii) the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 13 or 14, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 13 or 14.

In one example,

(i) the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19 or 20; and/or

(ii) the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 17 or 18, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 17 or 18.

In one example, at least one of the amino acid sequences under (i), (ii), (iii), (iv), or (v) 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. In one example, each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) 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.

In one example, at least one RNA is a modified RNA, in particular a stabilized mRNA. In one example, at least one RNA comprises a modified nucleoside in place of at least one uridine. In one example, at least one RNA comprises a modified nucleoside in place of each uridine. In one example, each RNA comprises a modified nucleoside in place of at least one uridine. In one example, each RNA comprises a modified nucleoside in place of each uridine. In one example, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

In one example, at least one RNA comprises the 5'-cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$. In one example, each RNA comprises the 5'-cap $m_2^{7,2'\text{-}O}Gpp_sp(5')G$.

In one example, at least one RNA comprises a 5'-UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 21. In one example, each RNA comprises a 5'-UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 21.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, the amino acid sequence enhancing antigen processing and/or presentation comprises an amino acid sequence corresponding to the transmembrane and cytoplasmic domain of a MHC molecule, preferably a MHC class I molecule.

In one example,

(i) the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 25, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 25; and/or

(ii) the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 24, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 24.

In one example, the amino acid sequence enhancing antigen processing and/or presentation further comprises an amino acid sequence coding for a secretory signal peptide.

In one example,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of SEQ ID NO: 23, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 23; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 22.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence which breaks immunological tolerance. In one example, each amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence which breaks immunological tolerance. In one example, the amino acid sequence which breaks immunological tolerance comprises helper epitopes, preferably tetanus toxoid-derived helper epitopes.

In one example,

(i) the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 27, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 27; and/or

(ii) the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 26, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 26.

In one example, at least one RNA comprises a 3'-UTR comprising the nucleotide sequence of SEQ ID NO: 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 28. In one example, each RNA comprises a 3'-UTR comprising the nucleotide sequence of SEQ ID NO: 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 28.

In one example, at least one RNA comprises a poly-A sequence. In one example, each RNA comprises a poly-A sequence. In one example, the poly-A sequence comprises at least 100 nucleotides. In one example, the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 29.

In one example, the RNA is formulated as a liquid, formulated as a solid, or a combination thereof. In one example, the RNA is formulated for injection. In one example, the RNA is formulated for intravenous administration. In one example, the RNA is formulated or is to be formulated as lipoplex particles. In one example, the RNA lipoplex particles are obtainable by mixing the RNA with liposomes.

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 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 prostate cancer.

In one example, provided herein is the composition or medical preparation described herein for pharmaceutical use. 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 prostate 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 a checkpoint modulator. In one example, the checkpoint modulator is an anti-PD1 antibody, an anti-CTLA-4 antibody, or a combination of an anti-PD1 antibody and an anti-CTLA-4 antibody.

In one example, provided herein is a method of treating prostate cancer in a subject comprising administering at least one RNA to the subject, wherein the at least one RNA encodes the following amino acid sequences:

(i) an amino acid sequence comprising Kallikrein-2 (KLK2), an immunogenic variant thereof, or an immunogenic fragment of the KLK2 or the immunogenic variant thereof;

(ii) an amino acid sequence comprising Prostate Specific Antigen (PSA), an immunogenic variant thereof, or an immunogenic fragment of the PSA or the immunogenic variant thereof;

(iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP), an immunogenic variant thereof, or an immunogenic fragment of the PAP or the immunogenic variant thereof;

(iv) an amino acid sequence comprising Homeobox B13 (HOXB13), an immunogenic variant thereof, or an immunogenic fragment of the HOXB13 or the immunogenic variant thereof; and

(v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1), an immunogenic variant thereof, or an immunogenic fragment of the NKX3-1 or the immunogenic variant thereof.

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

In one example,

(i) the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 3 or 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 3 or 4; and/or

(ii) the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 1 or 2, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 1 or 2.

In one example,

(i) the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 7 or 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 7 or 8; and/or

(ii) the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 5 or 6, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 5 or 6.

In one example,

(i) the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 11 or 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 11 or 12; and/or

(ii) the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 9 or 10, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 9 or 10.

In one example,

(i) the RNA encoding the amino acid sequence under (iv) comprises the nucleotide sequence of SEQ ID NO: 15 or 16, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 15 or 16; and/or

(ii) the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 13 or 14, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 13 or 14.

In one example,

(i) the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 20, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 19 or 20; and/or

(ii) the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 17 or 18, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 17 or 18.

In one example, at least one of the amino acid sequences under (i), (ii), (iii), (iv), or (v) 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. In one example, each of the amino acid sequences under (i), (ii),

(iii), (iv), or (v) 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.

In one example, at least one RNA is a modified RNA, in particular a stabilized mRNA. In one example, at least one RNA comprises a modified nucleoside in place of at least one uridine. In one example, at least one RNA comprises a modified nucleoside in place of each uridine. In one example, each RNA comprises a modified nucleoside in place of at least one uridine. In one example, each RNA comprises a modified nucleoside in place of each uridine. In one example, the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

In one example, at least one RNA comprises the 5'-cap $m_2^{7,2'-O}Gpp_sp(5')G$. In one example, each RNA comprises the 5'-cap $m_2^{7,2'-O}Gpp_sp(5')G$.

In one example, at least one RNA comprises a 5'-UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 21. In one example, each RNA comprises a 5'-UTR comprising the nucleotide sequence of SEQ ID NO: 21, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 21.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one example, each amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence enhancing antigen processing and/or presentation. In one

example, the amino acid sequence enhancing antigen processing and/or presentation comprises an amino acid sequence corresponding to the transmembrane and cytoplasmic domain of a MHC molecule, preferably a MHC class I molecule.

In one example,

(i) the RNA encoding the amino acid sequence enhancing antigen processing and/or presentation comprises the nucleotide sequence of SEQ ID NO: 25, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 25; and/or

(ii) the amino acid sequence enhancing antigen processing and/or presentation comprises the amino acid sequence of SEQ ID NO: 24, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 24.

In one example, the amino acid sequence enhancing antigen processing and/or presentation further comprises an amino acid sequence coding for a secretory signal peptide.

In one example,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of SEQ ID NO: 23, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 23; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 22.

In one example, at least one amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence which breaks immunological tolerance. In one example, each amino acid sequence under (i), (ii), (iii), (iv), or (v) comprises an amino acid sequence which breaks immunological tolerance. In one example, the amino acid sequence which breaks immunological tolerance comprises helper epitopes, preferably tetanus toxoid-derived helper epitopes.

In one example,

(i) the RNA encoding the amino acid sequence which breaks immunological tolerance comprises the nucleotide sequence of SEQ ID NO: 27, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 27; and/or

(ii) the amino acid sequence which breaks immunological tolerance comprises the amino acid sequence of SEQ ID NO: 26, or an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of SEQ ID NO: 26.

In one example, at least one RNA comprises a 3'-UTR comprising the nucleotide sequence of SEQ ID NO: 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 28. In one example, each RNA comprises a 3'-UTR comprising the nucleotide sequence of SEQ ID NO: 28, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 28.

In one example, at least one RNA comprises a poly-A sequence. In one example, each RNA comprises a poly-A sequence. In one example, the poly-A sequence comprises at least 100 nucleotides. In one example, the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 29.

In one example, the RNA is administered by injection. In one example, the RNA is administered by intravenous administration.

In one example, the RNA is formulated as lipoplex particles. In one example, the RNA lipoplex particles are obtainable by mixing the RNA with liposomes.

In one example, the subject is a human.

In one example, the method described herein 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 a checkpoint modulator. In one example, the checkpoint modulator is an anti-PD1 antibody, an anti-CTLA-4 antibody, or a combination of an anti-PD1 antibody and an anti-CTLA-4 antibody.

In one example, provided herein is RNA described herein, e.g.,
(i) RNA encoding an amino acid sequence comprising Kallikrein-2 (KLK2), an immunogenic variant thereof, or an immunogenic fragment of the KLK2 or the immunogenic variant thereof;
(ii) RNA encoding an amino acid sequence comprising Prostate Specific Antigen (PSA), an immunogenic variant thereof, or an immunogenic fragment of the PSA or the immunogenic variant thereof;

(iii) RNA encoding an amino acid sequence comprising Prostatic Acid Phosphatase (PAP), an immunogenic variant thereof, or an immunogenic fragment of the PAP or the immunogenic variant thereof;

(iv) RNA encoding an amino acid sequence comprising Homeobox B13 (HOXB13), an immunogenic variant thereof, or an immunogenic fragment of the HOXB13 or the immunogenic variant thereof; and/or

(v) RNA encoding an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1), an immunogenic variant thereof, or an immunogenic fragment of the NKX3-1 or the immunogenic variant thereof,

for use in a method described herein.

Brief description of the drawings

Figure 1: General structure of the RNAs RBL038.1, RBL039.1, RBL040.1, RBL041.1, and RBL045.1.

Schematic illustration of the general structures of all RNA vaccines with 5'-cap, 5'- and 3'-untranslated regions (UTRs), coding sequences with N- and C-terminal fusion tags (sec and P2P16/MITD, respectively) and poly(A)-tail. Please note that the individual elements are not drawn exactly true to scale compared to their respective sequence lengths.

Figure 2: 5'-capping structure beta-S-ARCA(D1) ($m_2^{7,2'\text{-}O}$GppSpG).

Shown in red are the differences between beta-S-ARCA(D1) and the basic cap analog m^7GpppG: an -OCH_3 group at the C2' position of the building block m^7G and substitution of a non-bridging oxygen at the beta-phosphate by sulfur. Owing to the presence of a stereogenic P center (labeled with asterisk), the phosphorothioate cap analog beta-S-ARCA exists as two diastereomers. Based on their elution order in reversed phase HPLC, these have been designated as D1 and D2.

Claims

1. A composition or medical preparation comprising RNA, wherein the RNA encodes the following amino acid sequences:
(i) an amino acid sequence comprising Kallikrein-2 (KLK2);
(ii) an amino acid sequence comprising Prostate Specific Antigen (PSA);
(iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP);
(iv) an amino acid sequence comprising Homeobox B13 (HOXB13); and
(v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1),
wherein each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) is encoded by a separate RNA, and each RNA comprises a 5'-cap, a 5'-UTR, a 3'-UTR and a poly-A sequence, wherein

the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 14, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 18, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 18.

2. The composition or medical preparation of claim 1, wherein

the amino acid sequence under (i) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 18.

3. The composition or medical preparation of claim 1 or 2, wherein

the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 18.

4. The composition or medical preparation of any one of claims 1 to 3, wherein

the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 4; and/or

the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 8; and/or

the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 12; and/or

the RNA encoding the amino acid sequence under (iv) comprises 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; and/or

the RNA encoding the amino acid sequence under (v) 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.

5. The composition or medical preparation of any one of claims 1 to 4, wherein at least one or each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) 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 does not change the sequence of the encoded amino acid sequence.

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

7. The composition or medical preparation of any one of claims 1 to 6, wherein the 5'-UTR comprises the nucleotide sequence of SEQ ID NO: 21.

8. The composition or medical preparation of any one of claims 1 to 7, wherein the 3'-UTR comprises the nucleotide sequence of SEQ ID NO: 28.

9. The composition or medical preparation of any one of claims 1 to 8, wherein the poly-A sequence comprises at least 100 nucleotides, or the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 29.

10. The composition or medical preparation of any one of claims 1 to 9, wherein the RNA is formulated for intravenous administration.

11. The composition or medical preparation of any one of claims 1 to 10, wherein the RNA is formulated or is to be formulated as lipoplex particles.

12. The composition or medical preparation of claim 11, wherein the RNA is formulated or is to be formulated as lipoplex particles which are obtainable by mixing the RNA with liposomes.

13. The composition or medical preparation of any one of claims 1 to 12, wherein the composition or medical preparation is

(i) a pharmaceutical composition; or

(ii) a kit.

14. The composition or medical preparation of claim 13, wherein the kit comprises the RNAs in separate vials or wherein the kit comprises the RNAs and liposomes in separate vials; and/or

wherein the kit further comprises instructions for use of the RNAs or the RNAs and liposomes for treating or preventing prostate cancer.

15. The composition or medical preparation of any one of claims 1 to 14 for use as a pharmaceutical.

16. Use of the composition or medical preparation of any one of claims 1 to 14 in the manufacture of a medicament for treating or preventing prostate cancer.

17. The composition or medical preparation of any one of claims 1 to 14, which is for administration to a human.

18. The use according to claim 16, wherein a further therapy is to be administered, wherein the further therapy comprises that a further therapeutic agent comprising an anti-cancer therapeutic agent and/or a checkpoint modulator is to be administered.

19. The use of claim 18, wherein the checkpoint modulator is an anti-PD1 antibody, an anti-CTLA-4 antibody, or a combination of an anti-PD1 antibody and an anti-CTLA-4 antibody.

20. Use of RNA in the manufacture of a medicament for treating prostate cancer in a subject, wherein the RNA encodes the following amino acid sequences:
(i) an amino acid sequence comprising Kallikrein-2 (KLK2);

(ii) an amino acid sequence comprising Prostate Specific Antigen (PSA);

(iii) an amino acid sequence comprising Prostatic Acid Phosphatase (PAP);

(iv) an amino acid sequence comprising Homeobox B13 (HOXB13); and

(v) an amino acid sequence comprising NK3 Homeobox 1 (NKX3-1),

wherein each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) is encoded by a separate RNA, and each RNA comprises a 5'-cap, a 5'-UTR, a 3'-UTR and a poly-A sequence, wherein

the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 2, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 6, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 14, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 18, or an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 18.

21. The use of claim 20, wherein

the amino acid sequence under (i) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises an amino acid sequence having at least 99%, 98%, 97%, 96%, or 95% identity to the amino acid sequence of SEQ ID NO: 18.

22. The use of claim 20 or 21, wherein

the amino acid sequence under (i) comprises the amino acid sequence of SEQ ID NO: 2;

the amino acid sequence under (ii) comprises the amino acid sequence of SEQ ID NO: 6;

the amino acid sequence under (iii) comprises the amino acid sequence of SEQ ID NO: 10;

the amino acid sequence under (iv) comprises the amino acid sequence of SEQ ID NO: 14; and

the amino acid sequence under (v) comprises the amino acid sequence of SEQ ID NO: 18.

23. The use of any one of claims 20 to 22, wherein

the RNA encoding the amino acid sequence under (i) comprises the nucleotide sequence of SEQ ID NO: 4, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 4; and/or

the RNA encoding the amino acid sequence under (ii) comprises the nucleotide sequence of SEQ ID NO: 8, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 8; and/or

the RNA encoding the amino acid sequence under (iii) comprises the nucleotide sequence of SEQ ID NO: 12, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, or 90% identity to the nucleotide sequence of SEQ ID NO: 12; and/or

the RNA encoding the amino acid sequence under (iv) comprises 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; and/or

the RNA encoding the amino acid sequence under (v) comprises the nucleotide sequence of SEQ ID NO: 19 or 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.

24. The use of any one of claims 20 to 23, wherein at least one or each of the amino acid sequences under (i), (ii), (iii), (iv), or (v) 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 does not change the sequence of the encoded amino acid sequence.

25. The use of any one of claims 20 to 24, wherein the 5'-cap is $m_2^{7,2'\text{-}O}Gpp_sp(5')G$.

26. The use of any one of claims 20 to 25, wherein the 5'-UTR comprises the nucleotide sequence of SEQ ID NO: 21.

27. The use of any one of claims 20 to 26, wherein the 3'-UTR comprises the nucleotide sequence of SEQ ID NO: 28.

28. The use of any one of claims 20 to 27, wherein the poly-A sequence comprises at least 100 nucleotides, or the poly-A sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 29.

29. The use of any one of claims 20 to 28,

wherein the RNA is to be administered by intravenous administration.

30. The use of any one of claims 20 to 29, wherein the RNA is formulated as lipoplex particles.

31. The use of any one of claims 20 to 30, wherein the subject is a human.

32. The use of any one of claims 20 to 30, which further comprises that a further therapy is to be administered, wherein the further therapy comprises that a further therapeutic agent comprising an anti-cancer therapeutic agent, and/or a checkpoint modulator is to be administered.

33. The use of claim 32, wherein the checkpoint modulator is an anti-PD1 antibody, an anti-CTLA-4 antibody, or a combination of an anti-PD1 antibody and an anti-CTLA-4 antibody.