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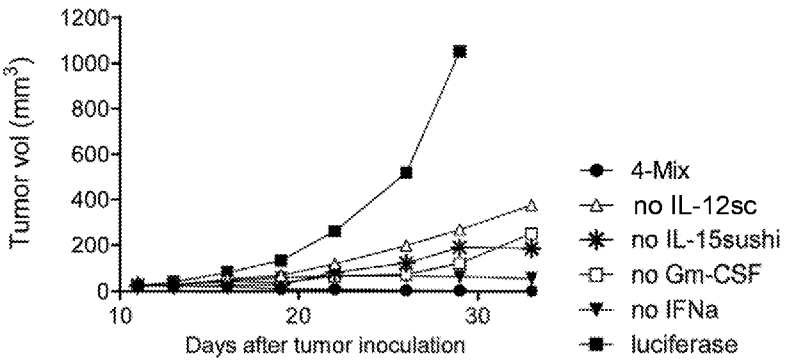

Fig. 1G

(57) Abstract: This disclosure relates to the field of therapeutic RNAs for treatment of solid tumor cancers.

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THERAPEUTIC RNA FOR SOLID TUMOR CANCERS

[0001] This application claims the benefit of priority to United States Provisional Application No. 62/722,742, filed August 24, 2018 and European Patent Application No. 19305092.9, filed January 24, 2019; the contents of both of which are incorporated by reference in their entireties.

[0002] This disclosure relates to the field of therapeutic RNA to treat solid tumors. The National Cancer Institute defines solid tumors as abnormal masses of tissue that do not normally contain cysts or liquid areas. Solid tumors include benign and malignant (cancerous) sarcomas, carcinomas, and lymphomas, and can be physically located in any tissue or organ including the brain, ovary, breast, colon, and other tissues. Cancer is often divided into two main types: solid tumor cancer and hematological (blood) cancers. It is estimated that more than 1.5 million cases of cancer are diagnosed in the United States each year, and more than 500,000 people in the United States will die each year from cancer.

[0003] Solid tumor cancers are particularly difficult to treat. Current treatments include surgery, radiotherapy, immunotherapy and chemotherapy. Surgery alone may be an appropriate treatment for small localized tumors, but large invasive tumors and most metastatic malignancies are usually unresectable by surgery. Other common treatments such as radiotherapy and chemotherapy are associated with undesirable side effects and damage to healthy cells.

[0004] While surgery and current therapies sometimes are able to kill the bulk of the solid tumor, additional cells (including potentially cancer stem cells) may survive therapy. These cells, over time, can form a new tumor leading to cancer recurrence. In spite of multimodal conventional therapies, disease-free survival is less than 25% for many types of solid tumors. Solid tumors that are resistant to multi-modal therapy or that have recurred following therapy are even more difficult to treat, and long-term survival is less than 10%.

[0005] Disclosed herein are compositions, uses, and methods that can overcome present shortcomings in treatment of solid tumors. Administration of therapeutic RNAs disclosed herein can reduce tumor size, extend survival time, and/or protect against metastasis and/or recurrence of the tumor.

SUMMARY

Embodiment 1 is a composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein.

Embodiment 2 is the medical preparation or composition according to embodiment 1, further comprising RNA encoding an FLT3-L protein.

Embodiment 3 is the composition according to embodiment 1 or 2.

Embodiment 4 is the medical preparation according to embodiment 1 or 2.

Embodiment 5 is the medical preparation or composition of any one of the preceding embodiments, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and optionally wherein the ratio is validated by quantitative RT-PCR.

Embodiment 6 is the medical preparation or composition of any one of the preceding embodiments, wherein the RNA integrity is greater than or equal to 70%.

Embodiment 7 is the medical preparation or composition of any one of the preceding embodiments, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.

Embodiment 8 is the medical preparation or composition of any one of the preceding embodiments, wherein the IFNα protein is an IFNα2b protein.

Embodiment 9 is the medical preparation or composition of any one of the preceding embodiments, wherein

the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18; and/or

the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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:14; and/or

the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

Embodiment 10 is the medical preparation or composition of any one of the preceding embodiments, wherein

the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26; and/or

the IL-15 sushi protein 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; and/or

the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

Embodiment 11 is the medical preparation or composition of any one of the preceding embodiments, wherein

the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or

the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

Embodiment 12 is the medical preparation or composition of any one of embodiments 2-11, wherein

the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

Embodiment 13 is the medical preparation or composition of any one of the preceding embodiments, wherein at least one RNA comprises a modified nucleoside in place of at least one uridine.

Embodiment 14 is the medical preparation or composition of any one of the preceding embodiments, wherein at least one RNA comprises a modified nucleoside in place of each uridine.

Embodiment 15 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises a modified nucleoside in place of at least one uridine.

Embodiment 16 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises a modified nucleoside in place of each uridine.

Embodiment 17 is the medical preparation or composition of any one of embodiments 13-16, wherein the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

Embodiment 18 is the medical preparation or composition of any one of embodiments 13-17, wherein at least one RNA comprises more than one type of modified nucleoside, wherein the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

Embodiment 19 is the medical preparation or composition of embodiment 18, wherein the modified nucleoside is N1-methyl-pseudouridine (m1ψ).

Embodiment 20 is the medical preparation or composition of any one of the preceding embodiments, wherein at least one RNA comprises the 5' cap $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG or 3′-O-Me-m^7G(5')ppp(5')G.

Embodiment 21 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises the 5' cap $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG or 3′-O-Me-m^7G(5')ppp(5')G.

Embodiment 22 is the medical preparation or composition of any one the preceding embodiments, wherein at least one RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.

Embodiment 23 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.

Embodiment 24 is the medical preparation or composition of any one of the preceding embodiments, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

Embodiment 25 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

Embodiment 26 is the medical preparation or composition of any one of the preceding embodiments, wherein at least one RNA comprises a poly-A tail.

Embodiment 27 is the medical preparation or composition of any one of the preceding embodiments, wherein each RNA comprises a poly-A tail.

Embodiment 28 is the medical preparation or composition of embodiment 26 or 27, wherein the poly-A tail comprises at least 100 nucleotides.

Embodiment 29 is the medical preparation or composition of any one of embodiments 26-28, wherein the poly-A tail comprises the poly-A tail shown in SEQ ID NO: 66.

Embodiment 30 is the medical preparation or composition of any one of the preceding embodiments, wherein one or more RNA comprises:

a 5' cap comprising $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$ or 3'-O-Me-$m^7G(5')ppp(5')G$;

a 5' UTR comprising (i) a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6;

a 3' UTR comprising (i) the nucleotide sequence of SEQ ID NO: 8, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO:8; and

a poly-A tail comprising at least 100 nucleotides.

Embodiment 31 is the medical preparation or composition of embodiment 30, wherein the poly-A tail comprises SEQ ID NO: 66.

Embodiment 32 is the medical preparation or composition of any one of the preceding embodiments, which is a pharmaceutical composition comprising the RNAs.

Embodiment 33 is the medical preparation or composition of embodiment 32, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

Embodiment 34 is the medical preparation or composition of any one of the preceding embodiments, wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof.

Embodiment 35 is the medical preparation or composition of any one of the preceding embodiments for pharmaceutical use.

Embodiment 36 is the medical preparation or composition of embodiment 35, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

Embodiment 37 is the medical preparation or composition of embodiment 36, wherein the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing a solid tumor.

Embodiment 38 is the medical preparation or composition of embodiment 37, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.

Embodiment 39 is the medical preparation or composition of any one of embodiments 37 or 38, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.

Embodiment 40 is the medical preparation or composition of any one of embodiments 37-39, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.

Embodiment 41 is the medical preparation or composition of any one of the preceding embodiments, wherein the RNA is for intra-tumoral or peri-tumoral administration.

Embodiment 42 is the medical preparation or composition of any one of the preceding embodiments, wherein the RNA is formulated for injection.

Embodiment 43 is the medical preparation or composition of any one of the preceding embodiments, which is for administration to a human.

Embodiment 44 is the medical preparation or composition of any one of embodiments 37-43, wherein treating or preventing the solid tumor comprises reducing the size of a tumor, preventing the reoccurrence of cancer in remission, or preventing cancer metastasis in a subject.

Embodiment 45 is the medical preparation or composition of any one of embodiments 36-44, wherein the therapeutic or prophylactic treatment of a disease or disorder further comprises administering a further therapy.

Embodiment 46 is the medical preparation or composition of embodiment 45, wherein the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) immunotherapy, (iii) radiotherapy, and (iv) chemotherapy.

Embodiment 47 is the medical preparation or composition of any one of embodiments 45-46, wherein the further therapy comprises administering a further therapeutic agent.

Embodiment 48 is the medical preparation or composition of embodiment 47, wherein the further therapeutic agent is an anti-cancer therapeutic agent.

Embodiment 49 is the medical preparation or composition of embodiment 47 or 48, wherein the further therapeutic agent is a checkpoint modulator.

Embodiment 50 is the medical preparation or composition of embodiment 49 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.

Embodiment 51 is a method for treating or reducing the likelihood of a solid tumor comprising administering to a subject in need thereof a first RNA, wherein the first RNA encodes an IL-12sc protein, an IL-15 sushi protein, an FLT3-L protein, or an IFNα protein and the subject is further treated with additional RNA, wherein:

if the first RNA encodes an IL-12sc protein, then the additional RNA encodes an IL-15 sushi protein, an IFNα protein, and a FLT3-L protein; or

if the first RNA encodes an IL-15 sushi protein, then the additional RNA encodes an IL-12sc protein, an IFNα protein, and a FLT3-L protein; or

if the first RNA encodes an IFNα protein, then the additional RNA encodes an IL-15 sushi protein, an IL-12sc protein, and a FLT3-L protein; or

if the first RNA encodes a FLT3-L protein, then the additional RNA encodes an IL-15 sushi protein, an IFNα protein, and an IL-12sc protein; or

if the first RNA encodes an IL-12sc protein, then the additional RNA encodes an IL-15 sushi protein and an IFNα protein; or

if the first RNA encodes an IL-15 sushi protein, then the additional RNA encodes an IL-12sc protein and an IFNα protein; or

if the first RNA encodes an IFNα protein, then the additional RNA encodes an IL-15 sushi protein and an IL-12sc protein.

Embodiment 52 is a kit comprising the composition of any one of embodiments 1-50.

Embodiment 53 is the medical preparation of any one of embodiments 1-2 or 4-50, wherein the medical preparation is a kit.

Embodiment 54 is the medical preparation of embodiment 53 or the kit of embodiment 52, wherein the RNAs are in separate vials.

Embodiment 55 is the kit of any one of embodiments 52-54, further comprising instructions for use of the composition for treating or preventing a solid tumor.

Embodiment 56 is RNA for use in a method for treating or preventing a solid tumor in a subject, wherein the method comprises administering RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein.

Embodiment 57 is use of RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein for the treatment of solid tumor.

Embodiment 58 is the RNA or use of any one of embodiments 56-57, further comprising RNA encoding an FLT3-L protein.

Embodiment 59 is the RNA or use of any one of embodiments 56-58, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and optionally wherein the ratio is validated by quantitative RT-PCR.

Embodiment 60 is the RNA or use of any one of embodiments 56-59, wherein the RNA integrity is greater than or equal to 70%.

Embodiment 61 is the RNA or use of any one of embodiments 56-60, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.

Embodiment 62 is the RNA or use of any one of embodiments 56-61, wherein the IFNα protein is an IFNα2b protein.

Embodiment 63 is the RNA or use of any one of embodiments 56-62, wherein

the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18 and/or

the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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: 14; and/or

the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

Embodiment 64 is the RNA or use of any one of embodiments 56-63, wherein

the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26 and/or

the IL-15 sushi protein 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; and/or

the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

Embodiment 65 is RNA or use of any one of embodiments 58-64, wherein

the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

Embodiment 66 is the RNA or use of any one of embodiments 56-65, wherein (i) the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or (ii) the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

Embodiment 67 is the RNA or use of any one of embodiments 56-66, wherein at least one RNA comprises a modified nucleoside in place of at least one uridine.

Embodiment 68 is the RNA or use of any one of embodiments 56-67, wherein at least one RNA comprises a modified nucleoside in place of each uridine.

Embodiment 69 is the RNA or use of any one of embodiments 56-68, wherein each RNA comprises a modified nucleoside in place of at least one uridine.

Embodiment 70 is the RNA or use of any one of embodiments 56-69, wherein each RNA comprises a modified nucleoside in place of each uridine.

Embodiment 71 is the RNA or use of any one of embodiments 67-70, wherein the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ) and 5-methyl-uridine (m5U).

Embodiment 72 is the RNA of any one of embodiments 67-71, wherein at least one RNA comprises more than one type of modified nucleoside, wherein the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).

Embodiment 73 is the RNA or use of embodiment 72, wherein the modified nucleoside is N1-methyl-pseudouridine (m1ψ).

Embodiment 74 is the RNA or use of any one of embodiments 56-73, wherein at least one RNA comprises the 5' cap m27,3'-OGppp(m12'-O)ApG or 3′-O-Me-m7G(5')ppp(5')G.

Embodiment 75 is the RNA or use of any one of embodiments 56-75, wherein at each RNA comprises the 5' cap m27,3'-OGppp(m12'-O)ApG or 3′-O-Me-m7G(5')ppp(5')G.

Embodiment 76 is the RNA or use of any one of embodiments 56-75, wherein at least one RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.

Embodiment 77 is the RNA or use of any one of embodiments 56-76, wherein each RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.

Embodiment 78 is the RNA or use of any one of embodiments 56-77, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

Embodiment 79 is the RNA or use of any one of embodiments 56-78, wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

Embodiment 80 is the RNA or use of any one of embodiments 56-79, wherein at least one RNA comprises a poly-A tail.

Embodiment 81 is the RNA or use of any one of embodiments 56-80, wherein each RNA comprises a poly-A tail.

Embodiment 82 is the RNA or use of embodiment 80 or 81, wherein the poly-A tail comprises at least 100 nucleotides.

Embodiment 83 is the RNA or use of any one of embodiments 80-82, wherein the poly-A tail comprises the poly-A tail shown in SEQ ID NO: 66.

Embodiment 84 is the RNA or use of any one of embodiments 56-83, wherein one or more RNA comprises:

a 5' cap comprising $m_2^{7,3'\text{-}O}Gppp(m_1^{2'\text{-}O})ApG$ or 3'-O-Me-m^7G(5')ppp(5')G;

a 5' UTR comprising (i) a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6;

a 3' UTR comprising (i) the nucleotide sequence of SEQ ID NO: 8, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO:8; and

a poly-A tail comprising at least 100 nucleotides.

Embodiment 85 is the RNA or use of embodiment 84, wherein the poly-A tail comprises SEQ ID NO: 66.

Embodiment 86 is the RNA or use of any one of embodiments 56-85, wherein the method further comprises administering a further therapy.

Embodiment 87 is the RNA or use of embodiment 86, wherein the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) immunotherapy, (iii) radiotherapy, and (iv) chemotherapy.

Embodiment 88 is the RNA or use of embodiment 86 or 87, wherein the further therapy comprises administering a further therapeutic agent.

Embodiment 89 is the RNA or use of embodiment 88, wherein the further therapeutic agent is an anti-cancer therapeutic agent.

Embodiment 90 is the RNA or use of embodiment 86 or 87, wherein the further therapeutic agent is a checkpoint modulator.

Embodiment 91 is the RNA or use of embodiment 90, 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.

Embodiment 92 is the RNA or use of any one of embodiments 56-91, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.

Embodiment 93 is the RNA or use of any one of embodiments 56-91, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.

Embodiment 94 is the RNA or use of any one of embodiments 56-93, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.

Embodiment 95 is the RNA or use of any one of embodiments 56-94, wherein the RNA is administered intra-tumorally or peri-tumorally.

Embodiment 96 is the RNA or use of any one of embodiments 56-95, wherein the RNA is formulated for injection.

Embodiment 97 is the RNA or use of any one of embodiments 86-96, wherein the further therapeutic agent is administered systemically.

Embodiment 98 is the RNA or use of any one of embodiments 56-97, wherein the subject is a human.

Embodiment 99 is the RNA or use of any one of embodiments 56-98, wherein the RNAs are administered at the same time.

Embodiment 100 is the RNA or use of any one of embodiments 56-99, wherein the RNAs are administered via injection, wherein the RNAs are mixed together in liquid solution prior to injection.

Embodiment 101 is the RNA or use of any one of embodiments 56-100, wherein the RNAs are administered by administering a composition comprising a combination of the RNAs.

Embodiment 102 is the RNA or use of any one of embodiments 56-100, wherein treating or preventing a solid tumor comprises reducing the size of a tumor, preventing the reoccurrence of cancer in remission, or preventing cancer metastasis in a subject.

Embodiment 103 is a composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding an FLT3-L protein.

Embodiment 104 is the composition according to embodiment 103.

Embodiment 105 is the medical preparation according to embodiment 103.

Embodiment 106 is the medical preparation or composition according to embodiments 103-105, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and optionally wherein the ratio is validated by quantitative RT-PCR.

Embodiment 107 is the medical preparation or composition according to embodiments 103-106, wherein the RNA integrity is greater than or equal to 70%.

Embodiment 108 is the medical preparation or composition according to embodiments 103-107, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.

Embodiment 109 is the medical preparation or composition according to embodiments 103-108, wherein the IFNα protein is an IFNα2b protein.

Embodiment 110 is the medical preparation or composition according to embodiments 103-109, wherein

the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18; and/or

the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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:14; and/or

the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

Embodiment 111 is the medical preparation or composition according to embodiments 103-110, wherein

the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26; and/or

the IL-15 sushi protein 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; and/or

the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

Embodiment 112 is the medical preparation or composition of according to embodiments 103-111, wherein

the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or

the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

Embodiment 113 is the medical preparation or composition according to embodiments 103-112, wherein

the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

Embodiment 114 is the medical preparation or composition according to embodiments 103-113, which is a pharmaceutical composition comprising the RNAs.

Embodiment 115 is the medical preparation or composition of embodiment 114, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

Embodiment 116 is the medical preparation or composition according to embodiments 103-115, wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof.

Embodiment 117 is the medical preparation or composition according to embodiments 103-116, for pharmaceutical use.

Embodiment 118 is the medical preparation or composition according to embodiments 103-117, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

Embodiment 119 is the medical preparation or composition according to embodiments 103-118, wherein the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing a solid tumor.

Embodiment 120 is the medical preparation or composition of embodiment 119, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.

Embodiment 121 is the medical preparation or composition of according to embodiments 119-120, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.

Embodiment 122 is the medical preparation or composition of according to embodiments 103-121, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.

Embodiment 123 is RNA for use in a method for treating or preventing a solid tumor in a subject, wherein the method comprises administering RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding a FLT3-L protein.

Embodiment 124 is use of RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding an FLT3-L for the treatment of solid tumor.

Embodiment 125 is a composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an INFα protein (such as described herein) wherein

a. the RNA encoding an IL-12sc protein is not RNA encoding an IL-12sc protein having at least 95% identity to the amino acid sequence of SEQ ID NO: 14, and/or does not comprise nucleotides having at least 95% identity to the nucleotides of SEQ ID NOs: 17 or 18;

b. the RNA encoding an IFNα2b protein is not RNA encoding an IFNα2b protein having at least 95% identity to the amino acid sequence of SEQ ID NO: 19, and/or does not comprise nucleotides having at least 95% identity to the nucleotides of SEQ ID NOs: 22 or 23; and

c. the RNA encoding an IL-15 sushi protein is not RNA encoding an IL-15 sushi protein having at least 95% identity to the amino acid sequence of SEQ ID NO: 24, and/or does not comprise nucleotides having at least 95% identity to the nucleotides of SEQ ID NO: 26.

FIGURE LEGENDS

[0006] FIGS 1A – 1H show results of experiments where CT26 tumor bearing mice were injected intratumorally with RNA (10 μg RNA/target or 40 μg of control RNA) on days

12, 15, 19 and 22 and individual tumor growth was monitored and plotted to day 35. FIG 1A shows results from treatment with a mixture of RNA encoding IL-15 sushi, IL-12sc, GM-CSF and IFNα. FIG 1B shows treatment with an RNA mixture of IL-15 sushi, IL-12sc and IFNα (no GM-CSF). FIG 1C shows treatment with an RNA mixture of IL-15 sushi, GM-CSF and IFNα (no IL-12sc). FIG 1D shows treatment with an RNA mixture of IL-12sc, GM-CSF and IFNα (no IL-15 sushi). FIG 1E shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, and GM-CSF (no IFNα). FIG 1F shows treatment with control RNA encoding luciferase. FIG 1G shows mean tumor volumes for each treatment group up to day 33. FIG 1H shows tumor growth repression to day 19 for each treatment group.

[0007] FIGS 2A – 2C show results of experiments where B16F10 tumor bearing mice were injected intratumorally with RNA (2 μg RNA/target or 8 μg of control RNA) on day 11 and individual tumor growth was monitored and plotted to day 62. FIG 2A shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, GM-CSF, and IFNα; FIG 2C shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, and IFNα (no GM-CSF); and FIG 2C shows luciferase control.

[0008] FIGS 3A – 3E show results of experiments where CT26 tumor bearing mice were injected intratumorally with RNA (5 μg RNA/target or 20 μg RNA control) on days 13, 16, 20, and 24 (A-B) or on day 11, 14, 17, and 21 (C-D) and individual tumor growth was monitored and plotted to day 50. FIGs 3A and 3C show treatment with an RNA mixture of IL-15 sushi, IL-12sc, IFNα, and FLT3-L. FIGs 3B and 3D show luciferase controls. FIG 3E shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, IFNα, and GM-CSF.

[0009] FIGS 4A – 4C show results of experiments where B16F10 tumor bearing mice were injected intratumorally with RNA (2 μg RNA/target or 8 μg of control RNA) on day 11 and individual tumor growth was monitored and plotted to day 57. FIG 4A shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, IFNα, and GM-CSF; FIG 4B shows treatment with an RNA mixture of IL-15 sushi, IL-12sc, IFNα, and FLT3-L; and FIG 4C shows luciferase control.

[0010] FIGS 5A – 5B show results of experiments where B16F10 tumor bearing mice were injected intratumorally with RNA (2 μg RNA/target or 8 μg of control RNA) and 7 days following intratumoral injection the tumors were removed, dissociated and stained with a panel of antibodies to assess intratumoral immune populations. The number of CD8+ T cells and NK cells were enumerated for the different treatment groups.

[0011] FIGS 6A – 6C show results of experiments where CT26 tumor bearing mice were injected intratumorally with RNA (5 μg RNA/target or 20 μg of control RNA) and the percentage of gp70-specific CD8+ T-cells in blood 19 and 31 days after treatment was assessed. FIG 6A shows day 19 and FIG 6B show day 31 from the same experiment. In a separate study of similar design gp70-specific CD8+ T-cells were assessed in the blood on day 24 (FIG 6C).

DESCRIPTION OF THE SEQUENCES

[0012] Table 1 provides a listing of certain sequences referenced herein.

TABLE 1: DESCRIPTION OF SEQUENCES

SEQ ID NO:	Description	SEQUENCE
5′ UTR		
1	Not Used	
2	Not Used	
3	Exemplary 5′ UTR (DNA)	GGAATAAACTAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCC
4	Exemplary 5′ UTR (RNA)	GGAAUAAACUAGUCUCAACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCC
5	Exemplary Alternative 5′ UTR (DNA)	AGACGAACTAGTATTCTTCTGGTCCCCACAGACTCAGAGAGAACCCGCCACC
6	Exemplary Alternative 5′ UTR (RNA)	AGACGAACUAGUAUUCUUCUGGUCCCCACAGACUCAGAGAGAACCCGCCACC
3′ UTR		
7	Exemplary 3′ UTR (DNA)	CTCGAGCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCAGGTA TGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAATGCAGCTCAAAACGCTTAGC CTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACTAAGCTATACTAACCCCAGGGTTGGTC AATTTCGTGCCAGCCACACCGAGACCTGGTCCAGAGTCGCTAGCCGCGTCGCT
8	Exemplary 3′ UTR (RNA)	CUCGAGCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUUCCCGUCCUGGGUACCCCGAGUCUCCCCCGACCUCGGGUCCCAGGUA UGCUCCCACCUCCACCUGCCCCACUCACCACCUCUGCUAGUUCCAGACACCUCCCAAGCACGCAGCAAUGCAGCUCAAAACGCUUAGC CUAGCCACACCCCCACGGGAAACAGCAGUGAUUAACCUUUAGCAAUAAACGAAAGUUUAACUAAGCUAUACUAACCCCAGGGUUGGUC AAUUUCGUGCCAGCCACACCGAGACCUGGUCCAGAGUCGCUAGCCGCGUCGCU
9-13	Not used	
Il-12sc (human)		

14	Human IL-12sc (amino acid)	MCHQQLVISWFSLVFLASPLVAIWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVKEFGDAGQY TCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLS AERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTWST PHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSSSWSEWASVPCSGSSGGGGSPGGGSSRNLPVATPDP GMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMM ALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVT IDRVMSYLNAS
15	Human non-optimized IL-12sc (CDS DNA) *Sequence annotation* CAPS: p40 domain; CAPS: linker; **CAPS: p35 domain.**	ATGTGTCACCAGCAGTTGGTCATCTCTTGGTTTTCCCTGGTTTTTCTGGCATCTCCCCTCGTGGCCATATGGGAACTGAAGAAAGATG TTTATGTCGTAGAATTGGATTGGTATCCGGATGCCCCTGGAGAAATGGTGGTCCTCACCTGTGACACCCCTGAAGAAGATGGTATCAC CTGGACCTTGGACCAGAGCAGTGAGGTCTTAGGCTCTGGCAAAACCCTGACCATCCAAGTCAAAGAGTTTGGAGATGCTGGCCAGTAC ACCTGTCACAAAGGAGGCGAGGTTCTAAGCCATTCGCTCCTGCTGCTTCACAAAAAGGAAGATGGAATTTGGTCCACTGATATTTTAA AGGACCAGAAAGAACCCAAAAATAAGACCTTTCTAAGATGCGAGGCCAAGAATTATTCTGGACGTTTCACCTGCTGGTGGCTGACGAC AATCAGTACTGATTTGACATTCAGTGTCAAAAGCAGCAGAGGGTCTTCTGACCCCCAAGGGGTGACGTGCGGAGCTGCTACACTCTCT GCAGAGAGAGTCAGAGGGGACAACAAGGAGTATGAGTACTCAGTGGAGTGCCAGGAGGACAGTGCCTGCCCAGCTGCTGAGGAGAGTC TGCCCATTGAGGTCATGGTGGATGCCGTTCACAAGCTCAAGTATGAAAACTACACCAGCAGCTTCTTCATCAGGGACATCATCAAACC TGACCCACCCAAGAACTTGCAGCTGAAGCCATTAAAGAATTCTCGGCAGGTGGAGGTCAGCTGGGAGTACCCTGACACCTGGAGTACT CCACATTCCTACTTCTCCCTGACATTCTGCGTTCAGGTCCAGGGCAAGAGCAAGAGAGAAAGAAAGATAGAGTCTTCACGGACAAGA CCTCAGCCACGGTCATCTGCCGCAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGAGCGAATGGGC ATCTGTGCCCTGCAGTGGCTCTAGCGGAGGGGGAGGCTCTCCTGGCGGGGGGATCTAG**CAGAAACCTCCCCGTGGCCACTCCAGACCCA** **GGAATGTTCCCATGCCTTCACCACTCCCAAAACCTGCTGAGGGCCGTCAGCAACATGCTCCAGAAGGCCAGACAAACTCTAGAATTTT** **ACCCTTGCACTTCTGAGGAAATTGATCATGAAGATATCACAAAAGATAAAACCAGCACAGTGGAGGCCTGTTTACCATTGGAATTAAC** **CAAGAATGAGAGTTGCCTAAATTCCAGAGACCTCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGACCTCTTTTATGATG** **GCCCTGTGCCTTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAAGACCATGAATGCAAAGCTTCTGATGGATCCTA** **AGAGGCAGATCTTTCTAGATCAAAACATGCTGGCAGTTATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACA** **AAAATCCTCCCTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTCAGAATTCGGGCAGTGACT** **ATTGATAGAGTGATGACTATCTGAATGCTTCCTGATGA**

16	Human optimized IL-12sc (CDS DNA)	ATGTGTCACCAGCAGCTGGTGATCTCATGGTTCTCCCTGGTATTTCTGGCATCTCCTCTTGTCGCAATCTGGGAACTGAAGAAAGACG
		TGTATGTCGTTGAGCTCGACTGGTATCCGGATGCGCCTGGCGAGATGGTGGTGCTGACCTGTGACACCCCAGAGGAGGATGGGATCAC
		TTGGACCCTTGATCAATCCTCCGAAGTGCTCGGGTCTGGCAAGACTCTGACCATACAAGTGAAAGAGTTTGGCGATGCCGGGCAGTAC
		ACTTGCCATAAGGGCGGAGAAGTTCTGTCCCACTCACTGCTGCTGCACAAGAAAGAGGACGGAATTTGGAGTACCGATATCCTGA
		AAGATCAGAAAGAGCCCAAGAACAAAACCTTCTTGCGGTGCGAAGCCAAGAACTACTCAGGGAGATTTACTTGTTGGTGGCTGACGAC
		GATCAGCACCGATCTGACTTTCTCCGTGAAATCAAGTAGGGGATCATCTGACCCTCAAGGAGTCACATGTGGAGCGGCTACTCTGAGC
		GCTGAACGCGTAAGAGGGGACAATAAGGAGTACGAGTATAGCGTTGAGTGCCAAGAGGATAGCGCATGCCCCGCCGCCGAAGAATCAT
		TGCCCATTGAAGTGATGGTGGATGCTGTACACAAGCTGAAGTATGAGAACTACACAAGGCTCCTTCTTCATCCGTGACATCATCAAACC
	Sequence annotation CAPS: p40 domain; CAPS: linker; **CAPS: p35 domain.**	AGATCCTCCTAAGAACCTCCAGCTTAAACCTCTGAAGAACTCTAGACAGGTGGAAGTGTCTTGGGAGTATCCCGACACCTGGTCTACA
		CCACATTCCTACTTCAGTCTCACATTCTGCGTTCAGGTACAGGGCAAGTCCAAAAGGGAGAAGGATCGGGTCTTTACAGATAAAA
		CAAGTGCCACCGTTATATGCCGGAAGAATGCCTCTATTTCTGTGCGTGCGCAGGACAGATACTATAGCAGCTCTTGGAGTGAATGGGC
		CAGTGTCCCATGTTCAGGGTCATCCGGTGGTGGCGGCAGCCCCGGAGGCGGTAGCTCC**CAGAAATCTCCCTGTGGCTACACCTGATCCA**
		GGCATGTTTCCCTGTTTGCACCATAGCCAAAACCTCCTGAGAGCAGTCAGCAACATGCTCCAGAAAGCTAGACAAACACTGGAATTCT
		ACCCATGCACCTCCGAGGAAATAGATCACGAGGATATCACTAAGGACAAAACAAGCACTGTCGAAGCATGCCTTCCCTTGGAACTGAC
		AAAGAACGAGAGTTGCCTTAATTCAAGAGAAACACTCTTTCATTACAAACGGTAGCTGCTTGGCAAGCAGAAAAACATCTTTTATGATG
		GCCCTTTGTCTGAGCAGTATTTATGAGGATCTCAAAATGTACCAGGTGGAGTTTAAGACCATGAATGCCAAGCTGCTGATGGACCCAA
		AGAGACAGATTTTCCTCGATCAGAATATGCTGGCTGTGATTGATGAACTGATGCAGGCCTTGAATTTCAACAGCGAAACCGTTCCCCA
		GAAAAGCAGTCTTGAAGAACCTGACTTTTATAAGACCAAGATCAAACTGTGTATTCTCCTGCATGCCTTTAGAATCAGAGCAGTCACT
		ATAGATAGAGTGATGTCCTACCTGAATGCTTCCTGATGA
17	Human non-optimized IL-12sc (RNA encoding CDS)	AUGUGUCACCAGCAGUUGGUCAUCUCUUGGUUUUUCCUGGUUUUUCUGGCAUCUCCCCUCGUGGCCAUAUGGGAACUGAAGAAAGAUG
		UUUAUGUCGUAGAAUUGGAUUGGUAUCCGGAUGCCCCUGGAGAAAUGGUGGUCCUCACCUGUGACACCCCUGAAGAAGAUGGUAUCAC
		CUGGACCUUGGACCAGAGCAGUGAGAGGUCUUAGGCUCUGGCAAAACCCUGACCAUCCAAGUCAAAGAGUUUGGAGAUGCUGGCCAGUAC
		ACCUGUCACAAAGGAGGCGAGGUUCUAAGCCAUUCGCUCCUGCUGCUUCACAAAAAGGAAGAUGGAAUUUGGUCCACUGAUAUUUUAA
		AGGACCAGAAAGAACCCAAAAAUAAGACCUUUCUAAGAUGCGAGGCCAAGAAUUAUUCUGGACGUUUCACCUGCUGGUGGCUGACGAC
		AAUCAGUACUGAUUUGACAUUCAGUGUCAAAAGCAGCAGAGGGUCUUCUGACCCCCAAGGGGUGACGUGCGGAGCUGCUACACUCUCU
		GCAGAGAGAGUCAGAGGGGACAACAAGGAGUAUGAGUACUCAGUGGAGUGCCAGGAGGACAGUGCCUGCCCAGCUGCUGAGAGGAGUC
		UGCCCAUUGAGGUCAUGGUGGAUGCCGUUCACAAGCUCAAGUAUGAAAACUACACCAGCAGCUUCUUCAUCAGGGACAUCAUCAAACC
		UGACCCACCCAAGAACUUGCAGCUGAAGCCAUUAAAGAAUUCUCGGCAGGUGGAGGUCAGCGUGGGAGUACCCUGACACCUGGAGUACU
		CCACAUUCCUACUUCUCCCUGACAUUCUGCGUUCAGGUCCAAGGGCAAGAGCAAGAGAGAAAGAAGAUAGAGUCUUCACGGACAAGA
		CCUCAGCCACGGUCAUCUGCCGCAAAAAUGCCAGCAUUAGCGUGCGGGCCCAGGACCGCUACAUAUAGCUCAUCUUGGAGCGAAUGGGC
		AUCUGUGCCCUGCAGUGGCUCUAGCGGAGGGGAGGCUCUCCUGGCGGGGGAUCUAGCAGAAACCUCCCCCGUGGCCACUCCAGACCCA
		GGAAUGUUCCCAUGCCUUCACCACUCCCAAAACCUGCUGAGGGCCGUCAGCAACAUGCUCCCAGAAGGCCAGACAAACUCUAGAAUUUU
		ACCCUUGCACUUCUGAGGAAAUUGAUCAUGAAGAUAUCACAAAAGAUAAAAACCAGCACAGUGGAGGCCUGUUUACCAUUGGAAUUAAC
		CAAGAAUGAGAGUUGCCUAAAUUCCAGAGACCUCUUUCAUAACUAAUGGGAGUUGCCUGGCCUCCAGAAAGACCUCUUUUAUGAUGG
		GCCCUGUGCCUUAGUAUUUAUGAAGACUUGAAGAUGUACCAGGUGGAGUUCAAGACCAUGAAUGCAAAGCUUCUGAUGGAUCCUA
		AGAGGCAGAUCUUUCUAGAUCAAAACAUGCUGGCAGUUAUUGAUGAGCUGAUGCAGGCCCUGAAUUUCAACAGUGAGACUGUGCCACA
		AAAAUCCUCCCUUGAAGAACCGGAUUUUUAUAAAAACUAAAAUCAAGCUCUGCAUACUUCUUCAUGCUUUCAGAAUUCGGGCAGUGACU
		AUUGAUAGAGUGAUGAGCUAUCUGAAUGCUUCCUGAUGA

18	Human optimized IL-12sc (RNA encoding CDS)	AUGUGUCACCAGCAGCUGGUGAUCUCAUGGUUCUCCCUGGUAUUUCUGGCAUCUCCUCUUGUCGCAAUCUGGGAACUGAAGAAAGACG UGUAUGUCGUUGAGCUCGACUGGUAUCCGGAUGCGCCUGGCGAGAUGGUGGUGCUGACCUGUGACACCCCAGAGGAGGAUGGGAUCAC UUGGACCCUUGAUCAAUCCUCCGAAGUGCUCGGUCUGGCAAGACUCUGACCAUACAAGUGAAAGAGUUUGGCGAUGCCGGGCAGUAC ACUUGCCAUAAGGGCGGAGAAGUUCUGUCCCACUCACUGCUGCUGCACAAGAAAGAGGACGGAAUUUGGAGUACCGAUAUCCUGA AAGAUCAGAAAGAGCCCAAGAACAAAACCUUCUUGCGGUGCGAAGCCAAGAACUACUCAGGAGAUUUACUUGUUGGUGGCUGACGAC GAUCAGCACCGAUCUGACUUUCUCCCGUGAAAUCAAGUAGGGGAUCAUCUGACCCUCAAGGAGUCACAUGUGGAGCGCGCUACUCUGAGC GCUGAACGCGUAAGAGGGGACAAUAAGGAGUACGAGUAUAGCGUUGAGUGCCAAGAGGAUAGCGCAUGCCCCGCCGCCGAAGAAUCAU UGCCCAUUGAAGUGAUGGUGGAUGCUGUACACAAGCUGAAGUAUGAGAACUACACAAGCUCCUUCUUCAUCCGUGACAUCAUCAAACC AGAUCCUCCUAAGAACCUCCCAGCUUAAACCUCUGAAGAACUCUAGACAGGUGGAAGUGUCUUGGGAGUAUCCCGACACCUGGUCUACA CCACAUUCCUACUUCAGUCUCACAUUCUGCGUUCAGGUACAGGGCAAGUCCAAAAGGGAGAAGAGGAUCGGGUCUUUACAGAUAAAA CAAGUGCCACCGUUAUAUGCCGGAAGAAUGCCUCUAUUUCUGUGCGUGCGCAGGACAGAUACUAUAGCAGCUCUUGGAGUGAAUGGGC CAGUGUCCCAUGUUCAGGGUCAUCCGGUGGUGGCGGCAGCCCCGGAGGCGGUAGCUCCAGAAAUCUCCCUGUGGCUACACCUGAUCCA GGCAUGUUUCCCUGUUUGCACCCAUAGCCAAAACCUCCUGAGAGCAGUCAGCAACAUGCUCCAGAAAGCUAGACAAACACUGGAAUUCU ACCCAUGCACCUCCGAGGAAAUAGAUCACGAGGAUAUCACUAAGGACAAAACAAGCACUGUCGAAGCAUGCCUUCCCUUGGAACUGAC AAAGAACGAGAGUUGCCUUAAUUCAAGAGAAACAUCUUUCAUUACAAACGGUAGCUGCUUGGCAAGCAGAAAAACAUCUUUUAUGAUG GCCCUUUGUCUGAGCAGUAUUUAUGAGGAUCUCAAAAUGUACCAGGUGGAGUUUAAGACCAUGAAUGCCAAGCUGCUGAUGGACCCAA AGAGACAGAUUUUUCCUCGAUCAGAAUAUGCUGGCUGUGAUUGAUGAACUGAUGCAGGCCUUGAAUUUCAACAGCGAAACCGUUCCCCA GAAAAGCAGUCUUGAAGACCUGACUUUUUAUAAGACCAAGAUCAAACUGUGUAUUCUCCUGCAUGCCUUUAGAAUCAGAGCAGUCACU AUAGAUAGAGUGAUGUCCUACCUGAAUGCUUCCUGAUGA
IFNalpha2b (IFNα2b) (human)		
19	Human IFNα2b (amino acid)	MALTFALLVALLVLSCKSSCSVGCDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQQIFN LFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSL STNLQESLRSKE
20	Human non-optimized IFNα2b (CDS DNA)	ATGGCCTTGACCTTTGCTTTACTGGTGGCCCTCCTGGTGCTCAGCTGCAAGTCAACTGCTCTGTGGGCTGTGATCTGCCTCAAACCC ACAGCCTGGGTAGCAGGAGGACCTTGATGCTCCTGGCACAGATGAGGAGAATCTCTCTTTCTCCTGCTTGAAGGACAGACATGACTT TGGATTTCCCCAGGAGGAGTTGGCAACCAGTTCCAAAAGGCTGAAACCATCCCTGTCCTCCATGAGATGATCCAGCAGATCTTCAAC CTTTTCAGCACACAAAGGACTCATCTGCTGCTTGGGATGAGACCCTCCTAGACAAATTCTACACTGAACTCTACCAGCAGCTGAATGACC TGGAAGCCTGTGTGATACAGGGGGTGGGGGTGACAGAGACTCCCCTGATGAAGGAGGACTCCATTCTGGCTGTGAGGAAATACTTCCA AAGAATCACTCTCTATCTGAAAGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGATCTTTTTCTTTG TCAACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAATGATGA
21	Human optimized IFNα2b (CDS DNA)	ATGGCCCTGACTTTTGCCCTTCTCGTGGCTTTGTTGGTGCTGAGTTGCAAATCTTCCTGTAGTGTCGGATGTGATCTGCCTCAAACCC ACAGTCTGGGATCTAGGAGAACACTGATGCTGTTGGCACAGATGAGGAGAATTAGCCTCTTTTCCTGCCTGAAGGATAGACATGACTT CGGCTTTCCCCAAGAGGAGTTTGGCAATCAGTTCCAGAAAGCGGAAACGATTCCCGTTCTGCACGAGATGATCCAGCAGATCTTCAAC CTCTTTTCAACCAAAGACAGCTCAGCAGCCTGGGATGAGACACTGCTGGACAAATTCTACACAGAACTGTATCAGCAGCTTAACGATC TGGAGGCATGCGTGATCCAAGGGGTTGGTGTGACTGAAACTCCGCTTATGAAGGAGGACTCCATTCTGGCTGTACGGAAGTACTTCCA GAGAATAACCCTCTATCTGAAGGAGAAGAAGTACTCACCATGTGCTTGGGAAGTCGTGAGAGCCGAAATCATGAGATCCTTCAGCCTT AGCACCAATCTCCAGGAATCTCTGAGAAGCAAAGAGTGATGA

22	**Human non-optimized IFNα2b (RNA encoding CDS)**	AUGGCCUUGACCUUUGCUUUACUGGUGGCCUCCUGGUGCUCAGCUGCAAGUCAAGCUGCUCUGUGGGCUGUGAUCUGCCUCAAACCC ACAGCCUGGGUAGCAGGAGGACCUUGAUGCUCCUGGCACAGAUGAGGAGAAUCUCUCUUUUCCUCCUGCUUGAAGGACAGACAUGACUU UGGAUUUCCCCAGGAGAGGAGUUUGGCAACCAUCCCUGAAACCAUCCCUGUCCUCCAUGAGAUGAUCCAGCAGAUCUUCAAC CUUUUCAGCACAAAGGACUCAUCUGCUGCUUGGGAUGAGACCCUCCUAGACAAAUUCUACACUGAACUCUACCAGCAGCUGAAUGACC UGGAAGCCUGUGUGAUACAGGGGGUGGGGGUGACAGAGACUCCCCUGAUGAAGGAGGACUCCAUUCUGGCUGUGAGGAAAUACUUCCA AAGAAUCACUCUCUAUCUGAAAGAGAAGAAAUACAGCCCUUGUGCCUGGGAGGUUGUCAGAGCAGAAAUCAUGAGAUCUUUUUCUUUG UCAACAAACUUGCAAGAAAGUUUAAGAAGUAAGGAAUGAUGA
23	**Human optimized IFNα2b (RNA encoding CDS)**	AUGGCCCUGACUUUUUGCCCUUCUCGUGGCUUUGUUGGUGCUGAGUUGCAAAUCUUCCUGUAGUGUCGGAUGUGAUCUGCCUCAAACCC ACAGUCUGGGAUCUAGGAGAACACUGAUGCUGUUGGCACAGAUGAGGAGAAUUAGCCUCUUUUCCUGCCUGAAGGAUAGACAUGACUU CGGCUUUCCCCCAAGAGGAGUUUGGCAAUCAGUUCCAGAAAGCGGAAACGAUUCCCGUUCUGCACGAGAUGAUCCAGCAGAUCUUCAAC CUCUUUUCAACCAAAGACAGCUCAGCAGCCUGGGAUGAGACACUGCUGGACAAAUUCUACACAGAACUGUAUCAGCAGCUUAACGAUC UGGAGGCAUGCGUGAUCCAAGGGGUUGGUGUGACUGAAACUCCGCUUAUGAAGGAGGACUCCAUUCUGGCUGUACGGAAGUACUUCCA GAGAAUAACCCUCUAUCUGAAGGAGAAGAAGUACUCCACCAUGUGCUUGGGAAGUCGUGAGAGCCGAAAUCAUGAGAUCCUUCAGCCUU AGCACCAAUCUCCAGGAAUCUCUGAGAAGCAAAGAGUGAUGA
IL-15 sushi (human)		
24	**Human IL-15 sushi (amino acid)**	MAPRRARGCRTLGLPALLLLLLRPPATRGITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTT PSLKCIRDPALVHQRPAPPGGGSGGGGSGGGGSLQNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQV ISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS
25	**Human IL-15 sushi (CDS DNA)** **Sequence annotations** CAPS: IL-15 sushi domain; CAPS: linker; **CAPS: mature IL-15**	ATGGCCCCCGCGGCGGCGGCGCTGCCGGACCCTCGGTCTCCCGGCGCTGCTACTGCTGCTCCGGCCGCCGCGACGCGGG GCATCACGTGCCCTCCCCCCATGTCCGTGGAACACGCAGACATCTGGGTCAAGAGCTACAGCTTGTACTCCAGGGAGCGGTACATTTG TAACTCTGGTTTCAAGCGTAAAGCCGGCACGTCCAGCCTGACGGAGTGCGTGTTGAACAAGGCCACGAATGTCGCCCACTGGACAACC CCCAGTCTCAAATGCATTAGAGACCCTGCCCTGGTTCACCAAAGGCCAGCGCCACCCGGGGGAGGATCTGGCGGCGGTGGGTCTGGCG GGGGATCTGGCGGAGGAGGAAGCTTACA**GAACTGGGTGAATGTAATAAGTGATTTGAAAAAATTGAAGATCTTTATTCAATCTATGCA** **TATTGATGCTACTTTATATACGGAAAGTGATGTTTCACCCCAGTTGCAAAGTAACAGCAATGAAGTGCTTTCTCTTGGAGTTACAAGTT** **ATTTCACTTGAGTCCGGAGATGCAAGTATTCATGATACAGTAGAAAATCTGATCATCCTAGCAAACACACAGTTTGTCTTCTAATGGGA** **ATGTAACAGAATCTGGATGCAAAGAATGTGAGGAACTGGAGGAAAAAATATTAAAGAATTTTTGCAGAGTTTTGTACATATTGTCCA** **AATGTTTCATCAACACTTCTTGATGA**

26	**Human IL-15 sushi (RNA encoding CDS)**	AUGGCCCCGCGGCGGCGCGCCGGACCUCGGUCUCCCGGCGCUGCUACUGCUGCUCCGGCCGCCGCGACGCGGG GCAUCACGUGCCCUCCCCCCCAUGUCCGUGGAACACGCAGACAUCUGGGUCAAGAGCUACAGCUUGUACUCCAGGGAGCGGUACAUUUG UAACUCUGGUUUCAAGCCGGCACGUCCAGCCUGACGGAGUGCGUGUUGAACAAGGCCACGAAUGUCGCCCACUGGACAACC CCCAGUCUCAAAUGCAUUAGAGACCCUGCCCUGGUUCACCAAAGGCCAGCGCCACCCGGGGAGGAUCUGGCGCGGUGGGUCUGGCG GGGGAUCUGGCGGAGGAGGAAGCUUACAGAACUGGGUGAAUGUAAUAAGUGAUUUGAAAAAAAUUGAAGAUCUUAUUCAAUCUAUGCA UAUUGAUGCUACUUUAUAUACGGAAAGUGAUGUUCACCCCAGUUGCAAAGUAACAGCAAUGAAGUGCUUUCUCUUGGAGUUACAAGUU AUUUCACUUGAGUCCGGAGAUGCAAGUAUUCAUGAUACAGUAGAAAAUCUGAUCAUCCUAGCAAACACAACAGUUUGUCUUCUAAUGGGA AUGUAACAGAAUCUGGAUGCAAAGAAUGUGAGGAGGAAAAAAAUAUUAAAGAAUUUUUGCAGAGUUUUGUACAUAUUGUCCA AAUGUUCAUCAACACUUCUUGAUGA
27-29	**Not used**	
FLT3-L (human)		
30	**Human FLT3-L (amino acid)**	MTVLAPAWSPTTYLLLLLLSSGLSGTQDCSFQHSPISSDFAVKIRELSDYLLQDYPVTV ASNLQDEELCGGLWRLVLAQRWMERLKTVAGSKMQGLLERVNTEIHFVTKCAFQPPPSCL RFVQTNISRLLQETSEQLVALKPWITRQNFSRCLELQCQPDSSTLPPPWSPRPLEATAPT APQPP
31	**Human FLT3L (CDS DNA)**	ATGACAGTGCTGGCGCCAGCCTGGAGCCCAACAACCTATCTCCTCCTGCTGCTGCTGAGCTCGGGACTCAGTGGGACCCAGGACT GCTCCTTCCAACACAGCCCCATCTCCTCCGACTTCGCTGTCAAAATCCGTGAGCTGTCTGACTACCTGCTTCAAGATTACCCAGTCAC CGTGGCCTCCAACCTGCAGGACGAGGAGCTCTGCGGGGGCCTCTGGCGGCTGGTCCTGGCACAGCGCTGGATGAGCGGCTCAAGACT GTCGCTGGGTCCAAGATGCAAGGCTTGCTGGAGCGCGTGAACACGGAGATACACTTTGTCACCAAATGTGCCTTTCAGCCCCCCCCA GCTGTCTTCGCTTCGTCCAGACCAACATCTCCCGCCTCCTGCAGGAGACCTCCGAGCAGCTGGTGGCGCTGAAGCCCTGGATCACTCG CCAGAACTTCTCCCGGTGCCTGGAGCTGCAGTGTCAGCCCGACTCCTCAACCCTGCCACCCCCATGGAGTCCCCGGCCCCTGGAGGCC ACAGCCCCGACAGCCCCGCAGCCCCCT
32	**Human FLT3L (RNA encoding CDS)**	AUGACAGUGCUGGCGCCAGCCUGGAGCCCAACAACCUAUCUCCUCCUGCUGCUGCUGAGCUCGGGACUCAGUGGGACCCAGGACU GCUCCUUCCAACACAGCCCCAUCUCCUCCGACUUCGCUGUCAAAAUCCGUGAGCUGUCUGACUACCUGCUUCAAGAUUACCCAGUCAC CGUGGCCUCCAACCUGCAGGACGAGGAGCUCUGCGGGGGCCUCUGGCGGCUGGUCCUGGCACAGCGCUGGAUGAGCGGCUCAAGACU GUCGCUGGGUCCAAGAUGCAAGGCUUGCUGGAGCGCGUGAACACGGAGAUACACUUUGUCACCAAAUGUGCCUUUCAGCCCCCCCCCA GCUGUCUUCGCUUCGUCCAGACCAACAUCUCCCGCCUCCUGCAGGAGACCUCCGAGCAGCUGGUGGCGCUGAAGCCCUGGAUCACUCG CCAGAACUUCUCCCGGUGCCUGGAGCUGCAGUGUCAGCCCGACUCCUCAACCCUGCCACCCCCAUGGAGUCCCCGGCCCCUGGAGGCC ACAGCCCCGACAGCCCCGCAGCCCCCU
IL-12sc (mouse)		
33-38	**not used**	

39	**Murine IL-12sc (amino acid)**	MGAMAPRTLLLLAAALAPTQTRAGPGSMWELEKDVYVVEVDWTPDAPGETVNLTCDTPEEDDITWTSDQRHGVIGSGKTLTITVKEF LDAGQYTCHKGGETLSHSHLLLHKKENGIWSTEILKNFKNKTFLKCEAPNYSGRFTCSWLVQRNMDLKFNIKSSSSSPDSRAVTCGMA SLSAEKVTLDQRDYEKYSVSCQEDVTCPTAEETLPIELALEARQQNKYENYSTSFFIRDIIKPDPPKNLQMKPLKNSQVEVSWEYPDS WSTPHSYFSLKFFVRIQRKKEKMKETEEGCNQKGAFLVEKTSTEVQCKGGNVCVQAQDRYYNSSCSKWACVPCRVRSVPGVGVPGVGR VIPVSGPARCLSQSRNLLKTTDDMVKTAREKLKHYSCTAEDIDHEDITRDQTSTLKTCLPLELHKNESCLATRETSSTTRGSCLPPQK TSLMMTLCLGSIYEDLKMYQTEFQAINAALQNHNHQQIILDKGMLVAIDELMQSLNHNGETLRQKPPVGEADPYRVKMKLCILLHAFS TRVVTINRVMGYLSSA
40	**Murine IL-12sc (DNA:5'UTR-CDS-3'UTR)**	GGAATAAACTAGTCTCAACACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCCATGGGCGCCATGGCCCCTAGAACATTGCTCC TGCTGCTGGCCGCTGCCCTGGCCCCTACACAGACAAGAGCTGGACCTGGATCCATGTGGGAGCTGGAGAAAGACGTTTATGTTGTAGA GGTGGACTGGACTCCCGATGCCCCTGGAGAAACAGTGAACCTCACCTGTGACACGCCTGAAGAAGATGACATCACCTGGACCTCAGAC CAGAGACATGGAGTCATAGGCTCTGGAAAGACCCTGACCATCACTGTCAAAGAGTTTCTAGATGCTGGCCAGTACACCTGCCACAAAG GAGGCGAGACTCTGAGCCACTCACATCTGCTGCTCCACAAGAAGGAAAATGGAATTTGGTCCACTGAAATTTTAAAAATTTCAAAAA CAAGACTTTCCTGAAGTGTGAAGCACCAAATTACTCCGGACGGTTCACGTGCTCATGGCTGGTGCAAAGAAACATGGACTTGAAGTTC AACATCAAGAGCAGTAGCAGTTCCCCTGACTCTCGGGCAGTGACATGTGGAATGGCGTCTCTGTCTGCAGAGAAGGTCACACTGGACC AAAGGGACTATGAGAAGTATTCAGTGTCCTGCCAGGAGGATGTCACCTGCCCAACTGCCGAGGAGACCCTGCCCATTGAACTGGCGTT GGAAGCACGGCAGCAGAATAAATATGAGAACTACAGCACCAGCTTCTTCATCAGGGACATCATCAAACCAGACCCGCCCAAGAACTTG CAGATGAAGCCTTTGAAGAACTCACAGGTGGAGGTCAGCTGGGAGTACCCTGACTCCTGGAGCACTCCCCATTCCTACTTCTCCCTCA AGTTCTTTGTTCGAATCCAGCGCCAAGAAAGAAAAGATGAAGGAGAGACAGAGGAGGGTGTAACCAGAAAGGTGCGTTCCTCGTAGAGAA GACATCTACCGAAGTCCAATGCAAAGGCGGGAATGTCTGCGTGCAAGCTCAGGATCGCTATTACAATTCCTCATGCAGCAAGTGGGCA TGTGTTCCCTGCAGATCCGGATCGGTTCCTGGAGTAGGGGTACCTGGAGTGGGCAGGGTCATACCGGTCTCTGGACCTGCCAGGTGTC TTAGCCAGTCCCGAAACCTGCTGAAGACCACAGATGACATGGTGAAGACGGCCAGAGAAAAGCTGAAACATTATTCCTGCACTGCTGA AGACATCGATCATGAAGACATCACACGGGACCAAACCAGCACACATTGAAGACCTGTTTACCACTGGAACTACACAAGAACGAGAGTTGC CTGGCTACTAGAGAGACTTCTTCCACAACAAGAGGGAGCTGCCTGCCCCCACAGAAGACGTCTTTGATGATGACCCTGTGCCTTGGTA GCATCTATGAGGACTTGAAGATGTACCAGACAGAGTTCCAGGCCATCAACGCAGCACTTCAGAATCACAACCATCAGCAGATCATTCT AGACAAGGGCATGCTGGTGGCCATCGATGAGCTGATGCAGTCTCTGAATCATAATGGCGAGACTCTGCGCCAGAAACCTCCTGTGGGA GAAGCAGACCCTTACAGAGTGAAAATGAAGCTCTGCATCCTGCTTCACGCCTTCAGCACCCGCGTCGTGACCATCAACAGGGTGATGG GCTATCTGTCCAGCGCCTAATAGCTCGACGTCCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAG TCTCCCCCGACCTCGGGTCCCAGGTATGCTCCCACCTCCACCTGCCCCCACTCACCACCTCTCGCTAGTTCCAGACACCTCCCAAGCACG CAGCAATGCAGCTCAAAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACT AAGCTATACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTCGAGCTAGC

41	Murine IL-12sc (RNA)	GGAAUAAACUAGUCUCAACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCCAUGGGCGCCCUAGAACAUUGCUCC UGCUGCUGGCCGCUGCCCCUACACAGACAAGAGCUGGACCUGGAUCCAUGUGGGAGCUGGAGAAAGACGUUUAUGUUGUAGA GGUGGACUGGACUCCCGAUGCCCCUGGAGAAACAGUGAACCUCACCUGUGACACGCCUGAAGAAGAUGACAUCACCUGGACCUCAGAC CAGAGACAUGGAGUCUAUAGGCUCUGGAAAGACCCUGACCAUCACUCUGUCAAAGAGUUUCUAGAUGCUGGCCAGUACACCUGCCACAAAG GAGGCGAGACUCUGAGCCACUCACAUCUGCUGCUCCCACAAGAAGGAAAAUGGAAUUUGGUCCACUGAAAUUUAAAAAAUUUCAAAAA CAAGACUUUCCUGAAGUGUGAAGCACCAAAUUACUCCGGACGGUUCACGUGCUCAUGGCUGGUGCAAAGAAACAUGGACUUGAAGUUC AACAUCAAGAGCAGUAGCAGUUCCCCUGACUCUCGGGCAGUGACAUGUGGAAUGGCGUCUCUGUCUGCAGAGAAGGUCACACUGGACC AAAGGGACUAUGAGAAGUAUUCAGUGUCCUGCCAGGAGGAUGUCACCUGCCCAACUGCCGAGGAGACCCUGCCCAUUGAACUGGCGUU GGAAGCACGGCAGCAGAAUAAAUAUGAGAACUACAGCACCAGCUUCUUCAUCAGGGACAUCAUCAACCAGACCCGCCCAAGAACUUG CAGAUGAAGCCUUUGAAGAACUCACAGGUGGAGGUCAGCUGGGAGUACCCUGACUCCUGGAGCACACUCCCCAUUCCUACUUCUCCCUCA AGUUCUUUGUUCGAAUCCAGCGCAAGAAAGAUGAAGAGACAGAGGAGGGUGUAACCAGAAAGGUGCGUUCCUCGUAGAGAA GACAUCUACCGAAGUCCAAUGCAAAGGCGGGAAUGUCUGCGUGCAAGCUCAGGAUCGCUAUUACAAUUCCUCAUGCAGCAAGUGGGCA UGUGUUCCCUGCAGAUCCGAUCGGUUCCUGGAGUAGGGGUACCUGGAGUGGGCAGGUCAUACCGGUCUCUGGACCUGCCAGGUGUC UUAGCCAGUCCCGAAACCUGCUGAAGACCACAGAUGACAUGGUGAAGACGGCCAGAGAAAAGCUGAAACAUUAUUCCUGCACUGCUGA AGACAUCGAUCAUGAAGACAUCACACGGGACCAAACCAGCACAUUGAAGACCUGUUUACCACUGGAACUACACAAGAACGAGAGUUGC CUGGCUACUAGAGACUUCUUCCACACAAGAGGGAGCUGCCUGCCCCCACAGAAGACGUCUUUGAUGAUGACCCUGUGCCUUGGUA GCAUCUAUGAGGACUUGAAGAUGUACCAGACAGAGUUCCAGGCCAUCAACGCAGCACUUCAGAAUCACAACCAUCAGCAGAUCAUUCU AGACAAGGGCAUGCUGGUGGCCAUCGAUGAGCUGAUGCAGUCUCUGAAUCAUAAUGGCGAGACUCUGCGCCAGAAACCUCCUGUGGGA GAAGCAGACCCUUACAGAGUGAAAAUGAAGCUCUGCAUCCUGCUUCACGCCCUUCAGCACCCGCGUCGUGACCAUCAACAGGGUGAUGG GCUAUCUGUCCAGCGCCUAAUAGCUCGACGUCCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUUCCCGUCCUGGGUACCCCGAG UCUCCCCCCGACCUCGGUCCCAGGUAUGCUCCCACACCUCCACCUGCCCCACUCACCACCUCUGCUAGUUCCAGACACCUCCCCAAGCACG CAGCAAUGCAGCUCUAGCCUAGCCACACCCCCACGGGAAACAGCAGUGAUUAACCUUUAGCAAUAAACGAAAGUUUAACU AAGCUAUACUAACCCCAGGGUUGGUCAAUUUCGUGCCAGCCACACCCUCGAGCUAGC
IFNα (IFNα4) mouse		
42-44	Not used	
45	Murine IFNα4 (amino acid)	MGAMAPRTLLLLAAALAPTQTRAGPGSCDLPHTYNLGNKRALTVLEEMRRLPPLSCLKDRKDFGFPLEKVDNQQIQKAQAILVLRDL TQQILNLFTSKDLSATWNATLLDSFCNDLHQQLNDLKACVMQEPPLTQEDSLLAVRTYFHRITVYLRKKKHSLCAWEVIRAEVWRALS SSTNLLARLSEEKE

46	**Murine IFNα4**	GGAATAAACTAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCCATGGGCGCCATGGCCCCTAGAACATTGCTCC TGCTGCTGGCCGCTGCCCCTGGCCCCTACACAGACAAGAGCTGGACCTGGATCCTGTGACCTGCCTCACACTTATAACCTCGGGAACAA GAGGGCCTTGACAGTCCTGGAAGAAATGAGAAGACTCCCCCCTCTTTCCTGCCTGAAGGACAGGAAGGATTTTGGATTCCCCTTGGAG AAGGTGGATAACCAACAGATCCAGAAGGCTCAAGCCATCCTTGTGCTAAGAGATCTTACCCAGCAGATTTTGAACCTCTTCACATCAA AAGACTTGTCTGCTACTTGGAATGCAACTCTCCTAGACTCATTCTGCAATGACCTCCATCAGCAGCTCAATGATCTCAAAGCCTGTGT GATGCAGGAACCTCCTCTGACCCAGGAAGACTCCCTGCTGGCTGTGAGGACATACTTCCACAGGATCACTGTGTACCTGAGAAAGAAG AAACACAGCCTCTGTGCCTGGGAGGTGATCAGAGCAGAAGTCTGGAGAGCCCTCTCTTCCTCAACCAACTTGCTGGCAAGACTGAGTG AGGAGAAGGAGTGATAACTCGACGTCCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCC CCGACCTCGGGTCCCAGGTATGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAA TGCAGCTCAAAACGCTTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACTAAGCTA TACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTCGAGCTAGC
47	**Murine IFNα4 (RNA)**	GGAAUAAACUAGUCUCAACACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCCAUGGGCGCCAUGGCCCCUAGAACAUUGCUCC UGCUGCUGGCCGCUGCCCCUGGCCCCUACACAGACAAGAGCUGGACCUGGAUCCUGUGACCUGCCUCACACUUAUAACCUCGGGAACAA GAGGGCCUUGACAGUCCUGGAAGAAAUGAGAAGACUCCCCCCCUCUUUCCUGCCUGAAGGACAGGAAGGAUUUUGGAUUCCCCUUGGAG AAGGUGGAUAACCAACAGAUCCAGAAGGCUCAAGCCAUCCUUGUGCUAAGAGAUCUUACCCAGCAGAUUUUGAACCUCUUCACAUCAA AAGACUUGUCUGCUACUUGGAAUGCAACUCUCCUAGACUCAUUCUGCAAUGACCUCCAUCAGCAGCUCAAUGAUCUCAAAGCCUGUGU GAUGCAGGAACCUCCUCUGACCCAGGAAGACUCCCUGCUGGCUGUGAGGACAUACUUCCACACGGAUCACUGUGUACCUGAGAAAGAAG AAACACAGCCUCUGUGCCUGGGAGGUGAUCAGAGCAGAAGUCUGGAGAGCCCUCUCUUCCUCAACCAACUUGCUGGCAAGACUGAGUG AGGAGAAGGAGUGAUAACUCGACGUCCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUUCCCGUCCUGGGUACCCCGAGUCUCCC CCGACCUCGGGUCCCAGGUAUGCUCCCACACCUGCCCCACUCACCACCUCUGCUAGUUCCAGACACCUCCCCAAGCACGCAGCAA UGCAGCUCAAAACGCUUAGCCUAGCCACACCCCCACGGGAAACAGCAGUGAUUAACCUUUAGCAAUAAACGAAAGUUUAACUAAGCUA UACUAACCCCAGGGUUGGUCAAUUUCGUGCCAGCCACACCCUCGAGCUAGC
IL-15 sushi mouse		
48-50	**Not used**	
51	**Murine IL-15 sushi (amino acid)**	MGAMAPRTLLLLAAALAPTQTRAGPGSTTCPPPVSIEHADIRVKNYSVNSRERYVCNSGFKRKAGTSTLIECVINKNTNVAHWTTPS LKCIRDPSLAGGSGGSGGSGGSGGSGGSGGNWIDVRYDLEKIESLIQSIHIDTTLYTDSDFHPSCKVTAMNCFLLELQVILHEYSNMT LNETVRNVLYLANSTLSSNKNVAESGCKECEELEEKTFTEFLQSFIRIVQMFINTS

52	**Murine IL-15 sushi (DNA:5'UTR-CDS-3'UTR)**	GGAATAAACTAGTCTCAACACAACATATACAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCCATGGCGCCATGGCCCCTAGAACATTGCTCC TGCTGCTGGCCGCTGCCCCTACACAGACAAGAGCTGGACCTGGATCCACACCACGTGTCCACCTCCCGTATCTATTGAGCATGC TGACATCCGGGTCAAGAATTACAGTGTGAACTCCAGGGAGAGGTATGTCTGTAACTCTGGCTTTAAGCGGAAAGCTGGAACATCCACC CTGATTGAGTGTGTGATCAACAAGAACACAAATGTTGCCCACTGGACAACTCCCAGCCTCAAGTGCATCAGAGACCCCTCCCTAGCTG GAGGGAGCGGAGGCTCTGGCGGAAGCGGCGGGTCTGGAGGCTCCGGGGGAAGCGGCGGAAATTGGATCGACGTGCGCTACGACCTGGA AAAGATCGAGAGCCTGATCCAGAGCATCCACATCGACACCACCCTGTACACCGACAGCGACTCCACCCCAGCTGCAAAGTGACCGCT ATGAACTGCTTCCTGCTGGAACTGCAAGTGATCCTGCACGAGTACAGCAACATGACCCTGAACGAGACAGTGCGGAACGTGCTGTACC TGGCCAACAGCACCCTGAGCAGCAACAAGAACGTGGCCGAGAGCGGCTGCAAAGAGTGCGAGGAACTGGAAGAAAGACCTTCACCGA GTTTCTGCAGAGCTTCATCAGGATCGTGCAGATGTTCATCAACACCTCTTGATGAGTCGACGTCCTGGTACTGCATGCACGCAATGCT AGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCAGGTATGCTCCCACCTCCCACCTGCCCCACTCACCA CCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAATGCAGCTCAAAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTG ATTAACCTTTAGCAATAAACGAAAGTTTAACTAAGCTATACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCCTCGAGCTAG C
53	**Murine IL-15 sushi (RNA:5'UTR-CDS-3'UTR))**	GGAAUAAACUAGUCUCAACACAACAUAUACAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCCAUGGGCGCCAUGGCCCCUAGAACAUUGCUCC UGCUGCUGGCCGCUGCCCUGGCCCCUACACAGACAAGAGCUGGACCUGGAUCCACCACGUGUCCACCUCCCGUAUCUAUUGAGCAUGC UGACAUCCGGGUCAAGAAUUACAGUGUGAACUCCAGGGAGAGGUAUGUCUGGCUUUAAGCGGAAAGCUGGAACAUCCACC CUGAUUGAGUGUGUGAUCAACAAGAACACAAAUGUUGCCCACUGGACAACUCCCAGCCUCAAGUGCAUCAGAGACCCCUCCCUAGCUG GAGGGAGCGGAGGCUCUGGCGGAAGCGGCGGGUCUGGAGGCUCCGGGGGAAGCGGCGGAAAUUGGAUCGACGUGCGCUACGACCUGGA AAAGAUCGAGAGCCUGAUCCAGAGCAUCCACATCGACACCACCCUGUACACCGACAGCGACUCCACCCCAGCUGCAAAGUGACCGCU AUGAACUGCUUCCUGCUGGAACUGCAAGUGAUCCUGCACGAGUACAGCAACAUGACCCUGAACGAGACAGUGCGGAACGUGCUGUACC UGGCCAACAGCACCCUGAGCAACAAGAACGUGGCCGAGAGCGGCUGCAAAGAGUGCGAGGAACUGGAAGAAAGACCUUCACCGA GUUUCUGCAGAGCUUCAUCAGGAUGUGCAGAUGUUCAUCAACACCUCUUGAUGAGUCGACGUCCUGGUACUGCAUGCACGCAAUGCU AGCUGCCCCUUUCCCGUCCUGGGUACCCCGAGUCUCCCCCGACCUCGGGUCCCAGGUAUGCUCCCACCUCCACCUGCCCCACUCACCA CCUCUGCUAGUUCCAGACACCUCCCAAGCACGCAGCAAUGCAGCUCAAAACGCUUAGCCUAGCCACACCCCCACGGGAAACAGCAGUG AUUAACCUUUAGCAAUAAACGAAAGUUUAACUAAGCUAUACUAACCCCAGGGUUGGUCAAUUUCGUGCCAGCCACACCCUCGAGCUAG C
GM-CSF mouse		
54-56	**Not used**	
57	**Murine GM-CSF (amino acid)**	MWLQNLLFLGIVVYSLSAPTRSPITVTRPWKHVEAIKEALNLLDDMPVTLNEEVEVVSNEFSFKKLTCVQTRLKIFEQGLRGNFTKLK GALNMTASYYQTYCPPTPETDCETQVTTYADFIDSLKTFLTDIPFECKKPGQK

58	**Murine GM-CSF**	GGAATAAACTAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCCATGTGGCTGCAGAACCTGCTGTTCCTGGGCA TCGTGGTGTACAGCCTGAGCGCCCCCACCAGGAGCCCCATCACCGTGACCAGGCCCTGGAAGCACGTGGAGGCCATCAAGGAGGCCCT GAACCTGCTGGACGACATGCCCGTGACCCTGAACGAGGAGGTGGAGGTGGTGAGCAACGAGTTCAGCTTCAAGAAGCTGACCTGCGTG CAGACCAGGCTGAAGATCTTCGAGCAGGGCCTGAGGGGCAACTTCACCAAGCTGAAGGGCGCCCTGAACATGACCGCCAGCTACTACC AGACCTACTGCCCCCCCACCCCCGAGACCGACTGCGAGACCCAGGTGACCACCTACGCCGACTTCATCGACAGCCTGAAGACCTTCCT GACCGACATCCCCTTCGAGTGCAAGAAGCCCGGCCAGAAGTGATGACTCGAGCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTT CCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCGGGTCCCAGGTATGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTT CCAGACACCTCCCAAGCACGCAGCAATGCAGCTCAAAACGCTTAGCCTACCACCCCCACGGGAAACAGCAGTGATTAACCTTTAG CAATAAACGAAAGTTTAACTAAGCTATACTAACCCCAGGGTTGGTCAATTTCGTGCCAGCCACACCGAGACCTGGTCCAGAGTCGCTA GCCGCGTCGCT
59	**Murine GM-CSF (RNA)**	GGAAUAAACUAGUCUCAACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCCAUGUGGCUGCAGAACCUGCUGUUCCUGGGCA UCGUGGUGUACAGCCUGAGCGCCCCCACCAGGAGCCCCAUCACCGUGACCAGGCCCUGGAAGCACGUGGAGGCCAUCAAGGAGGCCCU GAACCUGCUGGACGACAUGCCCGUGACCCUGAACGAGGAGGUGGAGGUGGUGAGCAACGAGUUCAGCUUCAAGAAGCUGACCUGCGUG CAGACCAGGCUGAAGAUCUUCGAGCAGGGCCUGAGGGGCAACUUCACCAAGCUGAAGGGCGCCCUGAACAUGACCGCCAGCUACUACC AGACCUACUGCCCCCCCACCCCGAGACCGACUGCGAGACCCAGGUGACCACCUACGCCGACUUCAUCGACAGCCUGAAGACCUUCCU GACCGACAUCCCCUUCGAGUGCAAGAAGCCCGGCCAGAAGUGAUGAGACUCGAGCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUU CCCGUCCUGGGUACCCCGAGUCUCCCCCGACCUCGGGUCCCAGGUAUGCUCCCACCUCCACCUGCCCCACUCACCACCUCUGCUAGUU CCAGACACCUCCCAAGCACGCAGCAAUGCAGCUCAAAACGCUUAGCCUAGCCACACCCCCACGGGAAACAGCAGUGAUUAACCUUUAG CAAUAAACGAAAGUUUAACUAAGCUAUACUAACCCCAGGGUUGGUCAAUUUCGUGCCAGCCACACCGAGACCUGGUCCAGAGUCGCUA GCCGCGUCGCU
FLT3-L (chimeric)		
60-62	**Not used**	
63	**FLT3-L (amino acid; human FLT3L in combination with a mouse optimized secretion sequence)**	MGAMAPRTLLLLLAAALAPTQTRAGPGSTQDCSFQHSPISSDFAVKIRELSDYLLQDYPVTVASNLQDEELCGGLWRLVLAQRWMERL KTVAGSKMQGLLERVNTEIHFVTKCAFQPPPSCLRFVQTNISRLLQETSEQLVALKPWITRQNFSRCLELQCQPDSSTLPPPWSPRPL EATAPTAPQPP

64	**FLT3-L (DNA; 5′UTR - human FLT3L in combination with a mouse optimized secretion sequence - 3′ UTR)**	GGAATAAACTAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCA TTTCTTTTAAAGCAAAAGCAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCCATGGGCGCCATGGCCCCTAGAACATTGCTCC TGCTGCTGGCCGCTGCCCTGGCCCCTACACAGACAAGAGCTGGACCTGGATCCACCCAGGACTGCAGCTTCCAGCACTCCCCTATCTC CTCCGACTTCGCCGTGAAGATCCGGGAGCTGTCCGATTACCTGCTGCAGGACTACCCTGTGACCGTGGCCAGCAACCTGCAGGACGAA GAACTGTGTGGCGGCCTGTGGCGGCTGGTGCTGGCCCAGCGGTGGATGGAACGGCTGAAAACCGTGGCCGGCTCCAAGATGCAGGGCC TGCTCGAGCGGGTGAACACCGAGATCCACTTCGTGACCAAGTGCGCCTTCCAGCCTCCTCCTTCCTGCCTGCGGTTCGTGCAGACCAA CATCTCCCGGCTGCTGCAGGAAACCTCCGAGCAGCTGGTCGCCCTGAAGCCTTGGATCACCCGGCAGAACTTCTCCCGGTGTCTGGAA CTCCAGTGTCAGCCCGACTCCTCCACCCTGCCTCCTCCCTGGTCCCCCAGGCCTCTGGAAGCCACCGCCCCTACCGCCCCACAGCCTC CTTGATAGGTCGACGTCCTGGTACTGCATGCACGCAATGCTAGCTGCCCCTTTCCCGTCCTGGGTACCCCGAGTCTCCCCCGACCTCG GGTCCCAGGTATGCTCCCACCTCCACCTGCCCCACTCACCACCTCTGCTAGTTCCAGACACCTCCCAAGCACGCAGCAATGCAGCTCA AAACGCTTAGCCTAGCCACACCCCCACGGGAAACAGCAGTGATTAACCTTTAGCAATAAACGAAAGTTTAACTAAGCTATACTAACCC CAGGGTTGGTCAATTTCGTGCCAGCCACACCCTCGAGCTAGC
65	**FLT3L (RNA; 5′UTR - human FLT3L in combination with a mouse optimized secretion sequence - 3′ UTR)**	GGAAUAAACUAGUCUCAACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCA UUUCUUUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGAUAGCCAUGGGCGCCAUGGCCCCUAGAACAUUGCUCC UGCUGCUGGCCGCUGCCCUGGCCCCUACACAGACAAGAGCUGGACCUGGAUCCACCCAGGACUGCAGCUUCCAGCACUCCCCUAUCUC CUCCGACUUCGCCGUGAAGAUCCGGGAGCUGUCCGAUUACCUGCUGCAGGACUACCCUGUGACCGUGGCCAGCAACCUGCAGGACGAA GAACUGUGUGGCGGCCUGUGGCGGCUGGUGCUGGCCCAGCGGUGGAUGGAACGGCUGAAAACCGUGGCCGGCUCCAAGAUGCAGGGCC UGCUCGAGCGGGUGAACACCGAGAUCCACUUCGUGACCAAGUGCGCCUUCCAGCCUCCUCCUUCCUGCCUGCGGUUCGUGCAGACCAA CAUCUCCCGGCUGCUGCAGGAAACCUCCGAGCAGCUGGUCGCCCUGAAGCCUUGGAUCACCCGGCAGAACUUCUCCCGGUGUCUGGAA CUCCAGUGUCAGCCCGACUCCUCCACCCUGCCUCCUCCCUGGUCCCCCAGGCCUCUGGAAGCCACCGCCCCUACCGCCCCACAGCCUC CUUGAUAGGUCGACGUCCUGGUACUGCAUGCACGCAAUGCUAGCUGCCCCUUUCCCGUCCUGGGUACCCCGAGUCUCCCCCGACCUCG GGUCCCAGGUAUGCUCCCACCUCCACCUGCCCCACUCACCACCUCUGCUAGUUCCAGACACCUCCCAAGCACGCAGCAAUGCAGCUCA AAACGCUUAGCCUAGCCACACCCCCACGGGAAACAGCAGUGAUUAACCUUUAGCAAUAAACGAAAGUUUAACUAAGCUAUACUAACCC CAGGGUUGGUCAAUUUCGUGCCAGCCACACCCUCGAGCUAGC
66	**Exemplary Poly-A**	AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCAUAUGACUAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAA
67-78	**Not used**	
79	**Anti-PD1 Mab heavy chain**	EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
80	**Anti-PD1 Mab light chain**	DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFRRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
81	**HCDR1**	GFTFSNFG

82	**HCDR2**	ISGGGRDT
83	**HCDR3**	VKWGNIYFDY
84	**LCDR1**	LSINTF
85	**LCDR2**	AAS
86	**LCDR3**	QQSSNTPFT
87	**Anti-PD1 Mab VH**	EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSS
88	**Anti-PD1 Mab VL**	DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFR

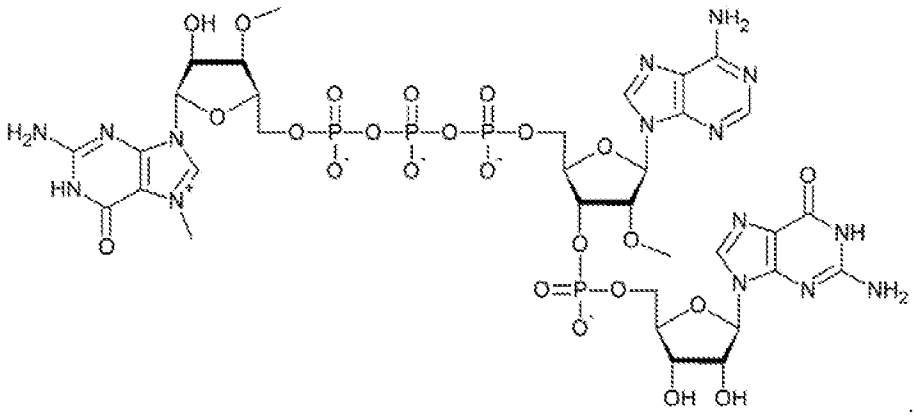
DETAILED DESCRIPTION

1. Definitions

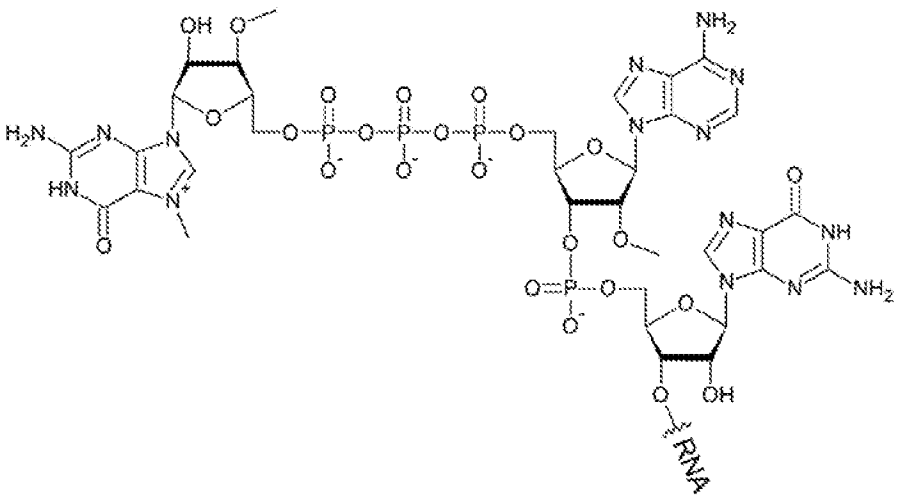
[0013] In some embodiments, the RNA comprises a modified nucleobase in place of at least one (e.g., every) uridine. In some embodiments, the RNA comprises a Cap1 structure at the 5' end of the RNA. In some embodiments, the RNA comprises a modified nucleobase in place of at least one (e.g., every) uridine and a Cap1 structure at the 5' end of the RNA. In some embodiments, the 5' UTR comprises SEQ ID NOs: 4 or 6. In some embodiments, the RNA has been processed to reduce double-stranded RNA (dsRNA), such as, for example, by purification on cellulose (as described in the Examples and as known in the art), or via high performance liquid chromatography (HPLC). The "Cap1" structure may be generated after in-vitro translation by enzymatic capping or during in-vitro translation (co-transcriptional capping).

[0014] In some embodiments, the building block cap for modified RNA is as follows, which is used when co-transcriptionally capping:

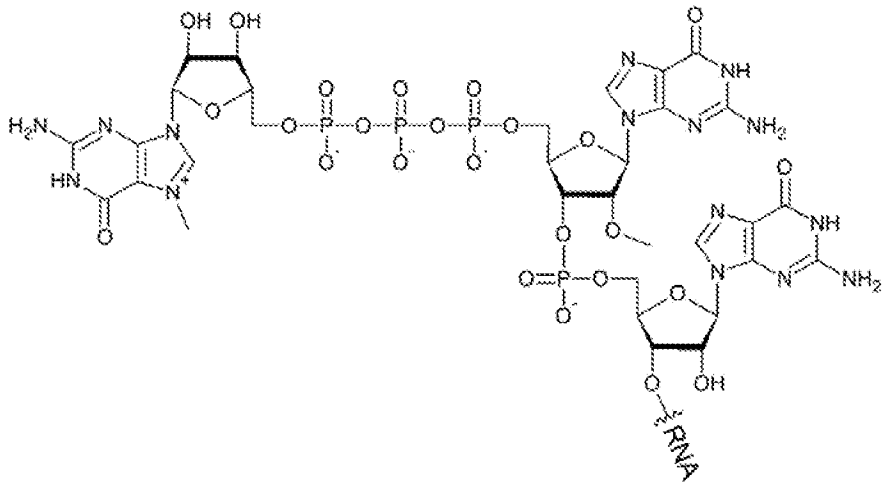
$m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG (also sometimes referred to as $m_2^{7,3'O}$G(5')ppp(5')$m^{2'\text{-}O}$ApG), which has the following structure:



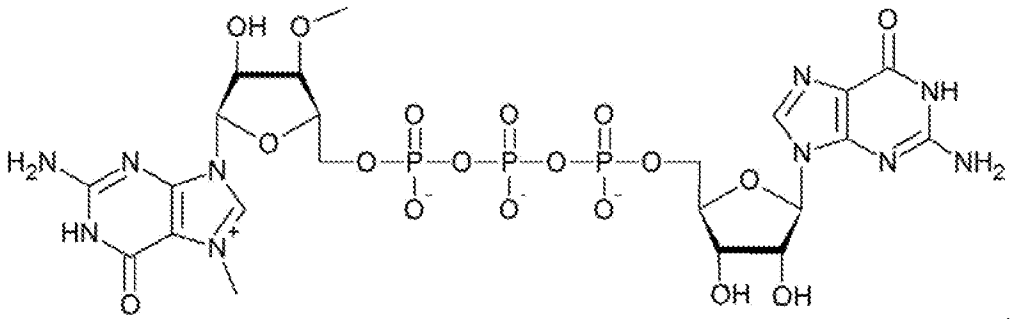
[0015] Below is an exemplary Cap1 RNA after co-transcriptional capping, which comprises RNA and $m_2^{7,3'O}$G(5')ppp(5')$m^{2'\text{-}O}$ApG:



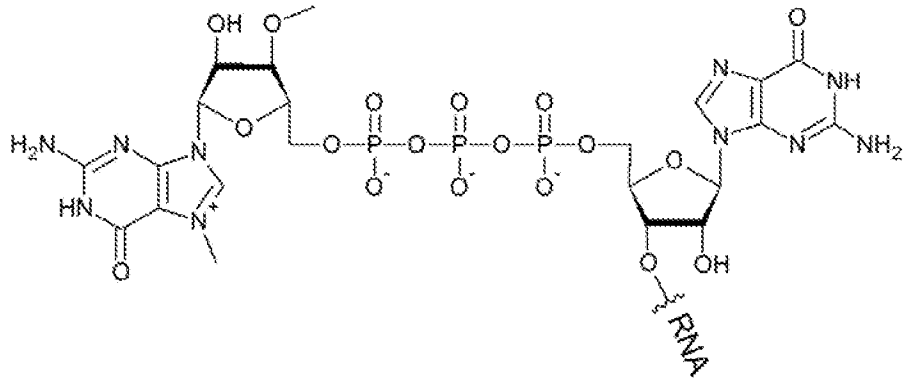
[0016] Below is another exemplary Cap1 RNA after enzymatic capping (no cap analog):



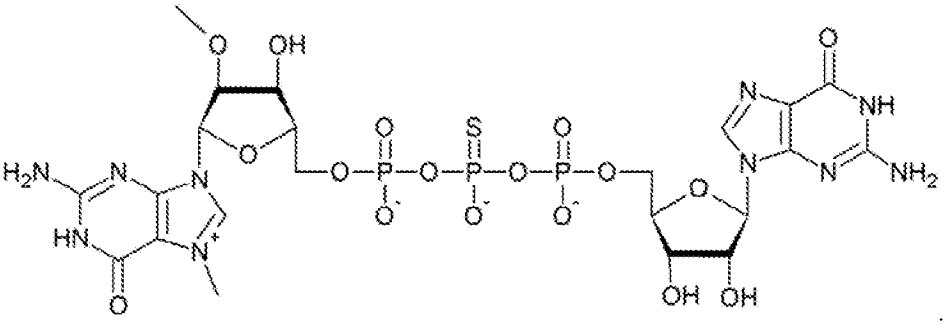
[0017] In some embodiments, the RNA is modified with "Cap0" structures generated during in-vitro translation (co-transcriptional capping) using, in one embodiment, the cap analog anti-reverse cap (ARCA Cap ($m_2^{7,3'O}$G(5')ppp(5')G)) with the structure:



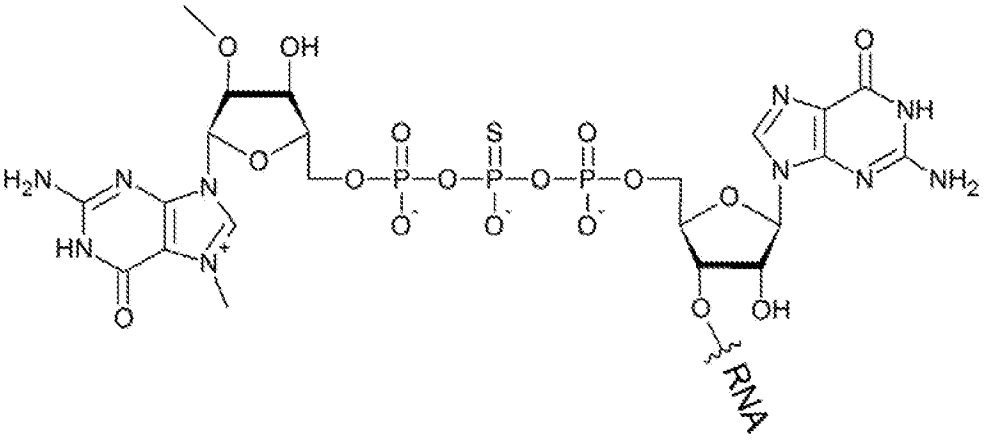
[0018] Below is an exemplary Cap0 RNA comprising RNA and $m_2^{7,3'O}$G(5')ppp(5')G:



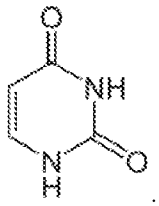
[0019] In some embodiments, the "Cap0" structures are generated during in-vitro translation (co-transcriptional capping) using the cap analog Beta-S-ARCA ($m_2^{7,2'O}$G(5')ppSp(5')G) with the structure:



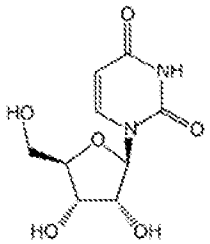
[0020] Below is an exemplary Cap0 RNA comprising Beta-S-ARCA ($m_2^{7,2'O}$G(5')ppSp(5')G) and RNA.



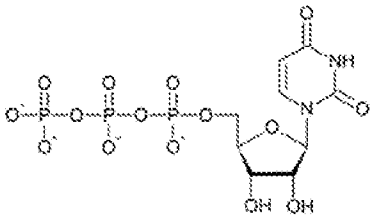
[0021] The term "uracil," as used herein, describes one of the nucleobases that can occur in the nucleic acid of RNA. The structure of uracil is:



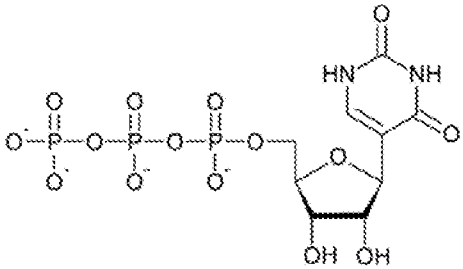
[0022] The term "uridine," as used herein, describes one of the nucleosides that can occur in RNA. The structure of uridine is:



[0023] UTP (uridine 5'-triphosphate) has the following structure:

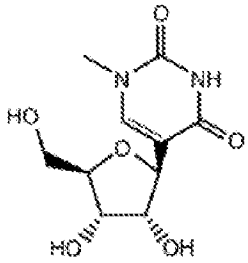


[0024] Pseudo-UTP (pseudouridine 5'-triphosphate) has the following structure:

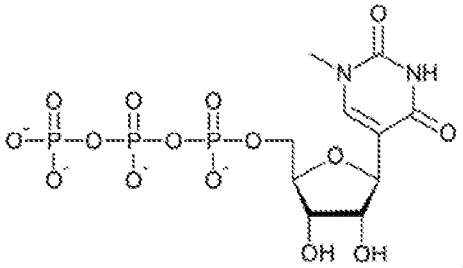


[0025] "Pseudouridine" is one example of a modified nucleoside that is an isomer of uridine, where the uracil is attached to the pentose ring via a carbon-carbon bond instead of a nitrogen-carbon glycosidic bond. Pseudouridine is described, for example, in Charette and Gray, *Life*; 49:341-351 (2000).

[0026] Another exemplary modified nucleoside is N1-methylpseudouridine (m1Ψ), which has the structure:



[0027] N1-Methylpseudo-UTP has the following structure:



[0028] As used herein, the term "poly-A tail" or "poly-A sequence" refers to an uninterrupted or interrupted sequence of adenylate residues which is typically located at the 3' end of an RNA molecule. Poly-A tails or poly-A sequences are known to those of skill in the art and may follow the 3' UTR in the RNAs described herein. An uninterrupted poly-A tail is characterized by consecutive adenylate residues. In nature, an uninterrupted poly-A tail is typical. RNAs disclosed herein can have a poly-A tail attached to the free 3' end of the RNA by a template-independent RNA polymerase after transcription or a poly-A tail encoded by DNA and transcribed by a template-dependent RNA polymerase.

[0029] It has been demonstrated that a poly-A tail of about 120 A nucleotides has a beneficial influence on the levels of RNA in transfected eukaryotic cells, as well as on the levels of protein that is translated from an open reading frame that is present upstream (5') of the poly-A tail (*Holtkamp et al.*, 2006, Blood, vol. 108, pp. 4009-4017).

[0030] The poly-A tail may be of any length. In one embodiment, a poly-A tail comprises, essentially consists of, or consists of at least 20, at least 30, at least 40, at least 80, or at least 100 and up to 500, up to 400, up to 300, up to 200, or up to 150 A nucleotides, and, in particular, about 120 A nucleotides. In this context, "essentially consists of" means that most nucleotides in the poly-A tail, typically at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% by number of nucleotides in the poly-A tail are A nucleotides, but permits that remaining nucleotides are nucleotides other than A nucleotides, such as U nucleotides (uridylate), G nucleotides

(guanylate), or C nucleotides (cytidylate). In this context, “consists of” means that all nucleotides in the poly-A tail, i.e., 100% by number of nucleotides in the poly-A tail, are A nucleotides. The term "A nucleotide" or "A" refers to adenylate.

[0031] In some embodiments, a poly-A tail is attached during RNA transcription, e.g., during preparation of in vitro transcribed RNA, based on a DNA template comprising repeated dT nucleotides (deoxythymidylate) in the strand complementary to the coding strand. The DNA sequence encoding a poly-A tail (coding strand) is referred to as poly(A) cassette.

[0032] In some embodiments, the poly(A) cassette present in the coding strand of DNA essentially consists of dA nucleotides but is interrupted by a random sequence of the four nucleotides (dA, dC, dG, and dT). Such random sequence may be 5 to 50, 10 to 30, or 10 to 20 nucleotides in length. Such a cassette is disclosed in WO 2016/005324 A1, hereby incorporated by reference. Any poly(A) cassette disclosed in WO 2016/005324 A1 may be used in the present invention. A poly(A) cassette that essentially consists of dA nucleotides, but is interrupted by a random sequence having an equal distribution of the four nucleotides (dA, dC, dG, dT) and having a length of e.g. 5 to 50 nucleotides shows, on DNA level, constant propagation of plasmid DNA in E.coli and is still associated, on RNA level, with the beneficial properties with respect to supporting RNA stability and translational efficiency is encompassed. Consequently, in some embodiments, the poly-A tail contained in an RNA molecule described herein essentially consists of A nucleotides but is interrupted by a random sequence of the four nucleotides (A, C, G, U). Such random sequence may be 5 to 50, 10 to 30, or 10 to 20 nucleotides in length.

[0033] In some embodiments, no nucleotides other than A nucleotides flank a poly-A tail at its 3' end, i.e., the poly-A tail is not masked or followed at its 3' end by a nucleotide other than A.

[0034] In some embodiments, a poly-A tail comprises the sequence:
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGCAUAUGACUAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAA (SEQ ID NO: 66), which is also shown in Table 1.

[0035] “RNA” and “mRNA” are used interchangeably herein.

[0036] “IFNα” is used generically herein to describe any interferon alpha Type I cytokine, including IFNα2b and IFNα4. Any IFNα may be incorporated into the compositions and used in the methods described herein.

[0037] The term “treatment,” as used herein, covers any administration or application of a therapeutic for disease in a subject, and includes inhibiting the disease, arresting its

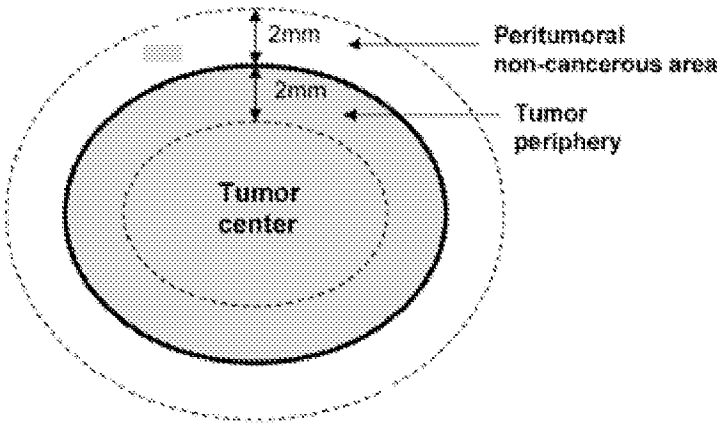
development, relieving one or more symptoms of the disease, curing the disease, or preventing reoccurrence of the disease. For example, treatment of a solid tumor may comprise alleviating symptoms of the solid tumor, decreasing the size of the solid tumor, eliminating the solid tumor, reducing further growth of the tumor, or reducing or eliminating recurrence of a solid tumor after treatment. Treatment may also be measured as a change in a biomarker of effectiveness or in an imaging or radiographic measure.

[0038] The term "prevention," as used herein, means inhibiting or arresting development of cancer, including solid tumors, in a subject deemed to be cancer free.

[0039] "Metastasis" means the process by which cancer spreads from the place at which it first arose as a primary tumor to other locations in the body.

[0040] The term "intra-tumorally," as used herein, means into the tumor. For example, intra-tumoral injection means injecting the therapeutic at any location that touches the tumor.

[0041] The term "peri-tumorally," or "peri-tumoral," as used herein, is an area that is about 2-mm wide and is adjacent to the invasive front of the tumor periphery. The peri-tumoral area comprises host tissue. See, for example:



[0042] "Administering" means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering.

[0043] The disclosure describes nucleic acid sequences and amino acid sequences having a certain degree of identity to a given nucleic acid sequence or amino acid sequence, respectively (a reference sequence).

[0044] "Sequence identity" between two nucleic acid sequences indicates the percentage of nucleotides that are identical between the sequences. "Sequence identity" between two amino acid sequences indicates the percentage of amino acids that are identical between the sequences.

[0045] The terms "% identical", "% identity" or similar terms are intended to refer, in particular, to the percentage of nucleotides or amino acids which are identical in an optimal alignment between the sequences to be compared. Said percentage is purely statistical, and the differences between the two sequences may be but are not necessarily randomly distributed over the entire length of the sequences to be compared. Comparisons of two sequences are usually carried out by comparing said sequences, after optimal alignment, with respect to a segment or "window of comparison", in order to identify local regions of corresponding sequences. The optimal alignment for a comparison may be carried out manually or with the aid of the local homology algorithm by Smith and Waterman, 1981, Ads App. Math. 2, 482, with the aid of the local homology algorithm by Neddleman and Wunsch, 1970, J. Mol. Biol. 48, 443, with the aid of the similarity search algorithm by Pearson and Lipman, 1988, Proc. Natl Acad. Sci. USA 88, 2444, or with the aid of computer programs using said algorithms (GAP, BESTFIT, FASTA, BLAST P, BLAST N and TFASTA in Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.).

[0046] Percentage identity is obtained by determining the number of identical positions at which the sequences to be compared correspond, dividing this number by the number of positions compared (e.g., the number of positions in the reference sequence) and multiplying this result by 100.

[0047] In some embodiments, the degree of identity is given for a region which is at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% or about 100% of the entire length of the reference sequence. For example, if the reference nucleic acid sequence consists of 200 nucleotides, the degree of identity is given for at least about 100, at least about 120, at least about 140, at least about 160, at least about 180, or about 200 nucleotides, in some embodiments in continuous nucleotides. In some embodiments, the degree of identity is given for the entire length of the reference sequence.

[0048] Nucleic acid sequences or amino acid sequences having a particular degree of identity to a given nucleic acid sequence or amino acid sequence, respectively, may have at least one functional property of said given sequence, e.g., and in some instances, are functionally equivalent to said given sequence. One important property includes the ability to act as a cytokine, in particular when administered to a subject. In some embodiments, a nucleic acid sequence or amino acid sequence having a particular degree of identity to a given nucleic acid sequence or amino acid sequence is functionally equivalent to said given sequence.

2. Compositions and Medical Preparations

[0049] In some embodiments, a composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein is provided. In some instances, the medical preparation or composition further comprises RNA encoding an FLT3-L protein.

[0050] In some embodiments, a composition comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein is provided.

[0051] In some embodiments, a medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein is provided.

[0052] In some embodiments, a composition comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and an RNA encoding an FLT3-L protein is provided.

[0053] In some embodiments, a medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and an RNA encoding an FLT3-L is provided.

[0054] In some embodiments, the medical preparation or composition comprises RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and optionally RNA encoding FLT3-L, wherein the RNA is in a mass ratio of 1:1:1 or 1:1:1:1 (when FLT3-L is present), optionally wherein the ratio is validated by quantitative RT-PCR or similar method. In some embodiments, the "RNA ratio" is determined by quantitative RT-PCR or similar method. In some embodiments, the RNA ratio is determined by 1) reverse transcribing the RNA mixture; and 2) quantifying each cDNA corresponding to each RNA in the mixture by droplet digital PCR (e.g., via the method of Bio-Rad) using Taqman-Probes. Based on the absolute count of positive events, the ratio of the individual sequences and thus, RNAs within the mixture is determined.

[0055] In some embodiments, the medical preparation or composition comprises RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and optionally RNA encoding FLT3-L, wherein the "RNA integrity" (i.e., percentage of intact RNA), is greater than or equal to 70%. In some embodiments, RNA integrity is the mass ratio percentage of full length RNA (i.e., non-degraded RNA) with respect to total RNA (i.e., full length RNA and degraded RNA). In some embodiments, the RNA integrity is determined using an Experion Automated Electrophoresis System (Bio-Rad) or similar

technology. In some embodiments, the RNA integrity is greater than or equal to 70, 71, 72, 73, 74, 75, 80, 85, 90, 95, 96, 97, 98, or 99%.

[0056] In some embodiments, each RNA in the composition or medical preparation is present in a length such that it produces the protein it encodes. In some embodiments, each RNA in the composition or medical preparation has an RNA integrity that maintains production of the protein encoded by the RNA.

[0057] In some embodiments, the medical preparation or composition comprises RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and optionally RNA encoding FLT3-L, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present. In some embodiment, the efficient removal of the DNA template is verified by qPCR or similar technology that targets a region within the DNA template. The residual amount of DNA template is then calculated based on a reference standard curve. In some embodiments, the medical preparation or composition comprises less than 250, 240, 230, 220, 210, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 ng DNA per the total mg of nucleic acid present.

[0058] In some embodiments, at least 95% of the composition or medical preparation comprises therapeutic RNA (e.g., RNA encoding therapeutic cytokines, checkpoint inhibitors, and/or other RNA intended to be therapeutic).

[0059] In some embodiments, the quantity of each RNA in the composition and medical preparation is enough to produce the protein it encodes.

[0060] In some embodiments, the quantity of each RNA in the composition and medical preparation is in an amount that when administered intra- or peri-tumorally, it contributes to the overall effect of treating or preventing a solid tumor cancer. That is, if an individual RNA in the composition or medical preparation were omitted from the composition or medical preparation, the treatment or prevention of solid tumor cancer would be reduced as compared to the composition or medical preparation comprising the omitted RNA.

[0061] In some embodiments, the quantity of each RNA in the composition and medical preparation is enough to produce in vitro biological effects essentially as follows:

The RNA is transfected into an appropriate cell line and the protein that the RNA encodes is expressed. The protein can be isolated, and bioactivity measured essentially as follows:

a) Activity of human IL-15 sushi can be determined by measuring proliferation of the CTLL-2 cell line (Paxton RJ. 2001. Measurement of interleukin 15. Curr Protoc

Immunol Chapter 6:Unit 6 22), which is a murine T-cell line growth-dependent on cytokines, such as IL-2, IL-15 or other common receptor γ-chain cytokine family members.

b) Activity of human IL-12sc can be determined via the IL-12-specific HEK-Blue cell line, HEK-Blue™ IL-12, which expresses alkaline phosphatase dependent on IL-12, measuring alkaline phosphatase activity (Breivik L, Oftedal BE, Boe Wolff AS, Bratland E, Orlova EM, Husebye ES. 2014. A novel cell-based assay for measuring neutralizing autoantibodies against type I interferons in patients with autoimmune polyendocrine syndrome type 1. Clin Immunol 153:220-227). The detection of the IL-12 bioactivity is based on the activation of the STAT4 pathway via IL-12 as the HEK-Blue™ IL-12 cells contain a STAT4-inducible SEAP (secreted embryonic alkaline phosphatase) reporter system.

c) Activity of human IFNα2b can be determined in IFNα-specific HEK-Blue cell line, HEK-Blue™ IFN-α/β, which expresses alkaline phosphatase dependent on IFNα, measuring alkaline phosphatase activity (Breivik et al.). The detection of the IFNα2b activity is based on the activation of the JAK-STAT pathway via type I interferons as the HEK-Blue™ IFN-a/ß cells contain a JAK-STAT-inducible SEAP reporter system.

d) Activity of FLT3-L can be determined by measuring the induction of IL-6 production in mouse myeloid leukemia M1 cells in the presence of mouse LIF recombinant Protein using ELISA based quantification of IL-6.

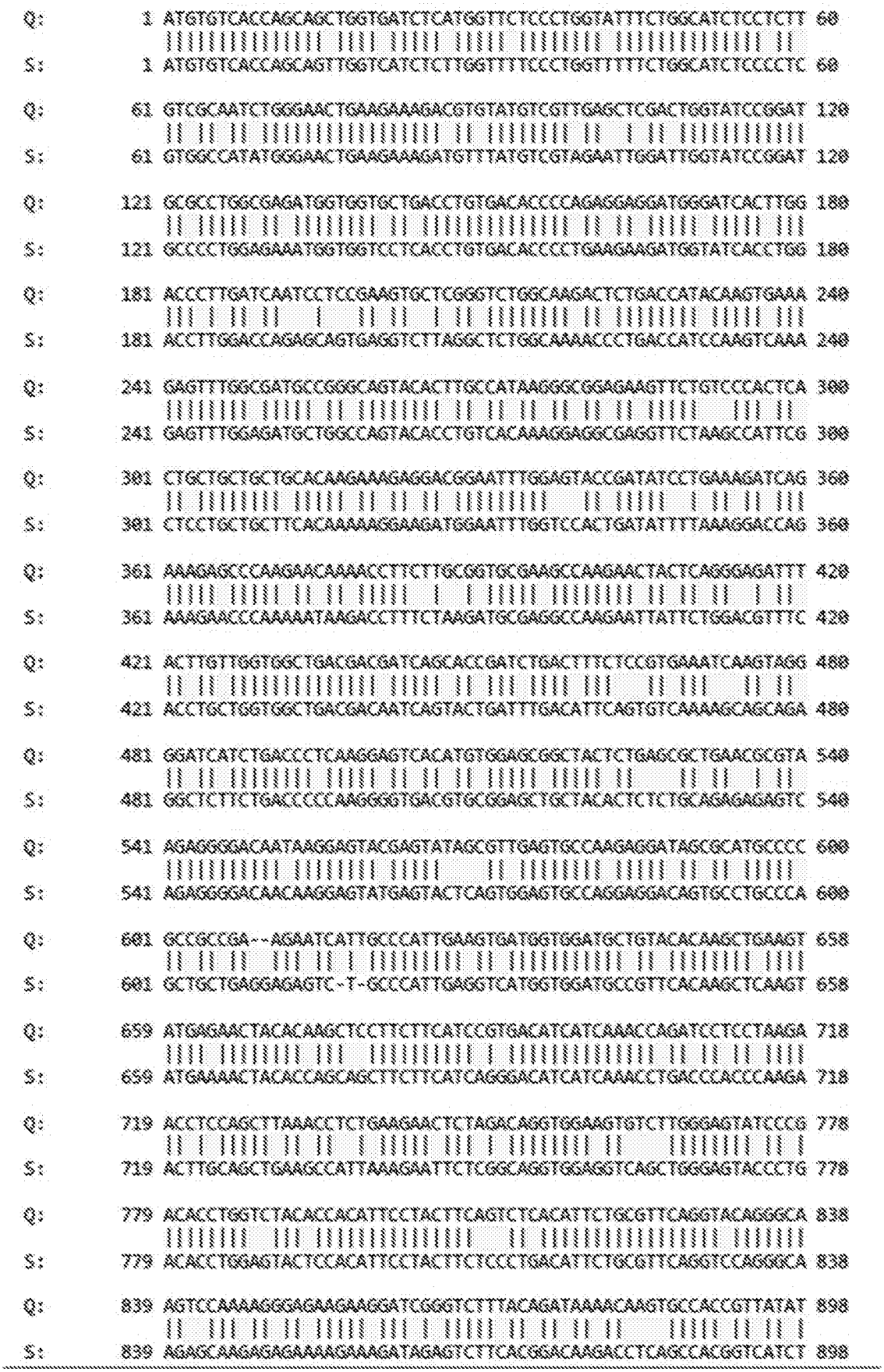
[0062] For each embodiment, the RNAs may be as described below and in Table 1.

A. Interleukin-12 single-chain (IL-12sc)

[0063] In some embodiments, a composition or medical preparation comprising RNA that encodes interleukin-12 single-chain (IL-12sc) is provided. In some embodiments, the interleukin-12 single-chain (IL-12sc) RNA is encoded by a DNA sequence encoding interleukin-12 single-chain (IL-12sc) (e.g., SEQ ID NO: 14), which comprises IL-12 p40 (sometimes referred to as IL-12B; encoded by nucleotides 1-984 of SEQ ID NO: 15), a linker, such as a GS linker, and IL-12 p35 (sometimes referred to as IL-12A; encoded by nucleotides 1027-1623 of SEQ ID NO: 15). In some embodiments, the IL-12p40, linker, and IL-12p35 are consecutive with no intervening nucleotides. An exemplary DNA sequence encoding IL-12sc is provided in SEQ ID NO: 15. In some embodiments, the interleukin-12 single-chain (IL-12sc) RNA is provided at SEQ ID NO: 17 or 18, both of which encode the protein of SEQ ID NO: 14. The RNA sequence of IL-12 p40 is shown at nucleotides 1-984 of

SEQ ID NO: 17 or 18 and the RNA sequence of IL-12 p35 is shown at nucleotides 1027-1623 of SEQ ID NO: 17 or 18.

[0064] The alignment of codon optimized IL-12 p40 to native IL-12 p40 is shown below, where the "S" is native IL-12 p40 (NM_002187.2; nucleotides 1-984 of SEQ ID NO: 15) and the "Q" is codon optimized IL-12 p40 (nucleotides 1-984 of SEQ ID NO: 16). The percent identity is 77%.



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Q:      899 GCCGGAAGAATGCCTCTATTTCTGTGCGTGCGCAGGACAGATACTATAGCAGCTCTTGGA 958
            |||| || ||||||   |||   ||||| || |||||| | |||||||||   |||||||
S:      899 GCCGCAAAAATGCCAGCATTAGCGTGCGGGCCCAGGACCGCTACTATAGCTCATCTTGGA 958

Q:      959 GTGAATGGGC--CAGTGTCCCATGTTCA 984
            | ||||||||  | ||| ||| ||  ||
S:      959 GCGAATGGGCATCTGTG-CCC-TG--CA 982
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[0065] The alignment of codon optimized IL-12 p35 to native IL-12 p35 is shown below, where the "S" is native IL-12 p35 (NM_00882.3; nucleotides 1027-1623 of SEQ ID NO: 15) and the "Q" is codon optimized IL-12 p35 (nucleotides 1027-1623 of SEQ ID NO: 16). The percent identity is 80%.

```
Q:        1 AGAAATCTCCCTGTGGCTACACCTGATCCAGGCATGTTTCCCTGTTTGCACCATAGCCAA 60
            ||||| ||||| ||||| || || || ||||| ||||| || ||  | |||||   ||||
S:        1 AGAAACCTCCCCGTGGCCACTCCAGACCCAGGAATGTTCCCATGCCTTCACCACTCCCAA 60

Q:       61 AACCTCCTGAGAGCAGTCAGCAACATGCTCCAGAAAGCTAGACAAACACTGGAATTCTAC 120
            ||||| ||||| || ||||||||||||||||||||| || |||||||| || ||||| |||
S:       61 AACCTGCTGAGGGCCGTCAGCAACATGCTCCAGAAGGCCAGACAAACTCTAGAATTTTAC 120

Q:      121 CCATGCACCTCCGAGGAAATAGATCACGAGGATATCACTAAGGACAAAACAAGCACTGTC 180
            || ||||| || || || || ||||| || |||||||| || || ||||| ||||| ||
S:      121 CCTTGCACTTCTGAAGAGATTGATCATGAAGATATCACAAAAGATAAAACCAGCACAGTG 180

Q:      181 GAAGCATGCCTTCCCTTGGAACTGACAAAGAACGAGAGTTGCCTTAATTCAAGAGAAACA 240
            || || ||  | || |||||| | || ||||| |||||||||| ||||| ||||| ||
S:      181 GAGGCCTGTTTACCATTGGAATTAACCAAGAATGAGAGTTGCCTAAATTCCAGAGAGACC 240

Q:      241 TCTTTCATTACAAACGGTAGCTGCTTGGCAAGCAGAAAAACATCTTTTATGATGGCCCTT 300
            |||||||| || || || || ||| ||||   |||||| || ||||||||||||||||||
S:      241 TCTTTCATAACTAATGGGAGTTGCCTGGCCTCCAGAAAGACCTCTTTTATGATGGCCCTG 300

Q:      301 TGTCTGAGCAGTATTTATGAGGATCTCAAAATGTACCAGGTGGAGTTTAAGACCATGAAT 360
            || || || |||||||||| ||  | || ||||||||||||||||| ||||||||||||
S:      301 TGCCTTAGTAGTATTTATGAAGACTTGAAGATGTACCAGGTGGAGTTCAAGACCATGAAT 360

Q:      361 GCCAAGCTGCTGATGGACCCAAAGAGACAGATTTTCCTCGATCAGAATATGCTGGCTGTG 420
            || ||||| |||||||| || ||||| ||||| || || ||||| || |||||||| ||
S:      361 GCAAAGCTTCTGATGGATCCTAAGAGGCAGATCTTTCTAGATCAAAACATGCTGGCAGTT 420

Q:      421 ATTGATGAACTGATGCAGGCCTTGAATTTCAACAGCGAAACCGTTCCCCAGAAAAGCAGT 480
            |||||||| |||||||||||| |||||||||||| || || || || || |||  |
S:      421 ATTGATGAGCTGATGCAGGCCCTGAATTTCAACAGTGAGACTGTGCCACAAAAATCCTCC 480

Q:      481 CTTGAAGAACCTGACTTTTATAAGACCAAGATCAAACTGTGTATTCTCCTGCATGCCTTT 540
            |||||||||| || |||||||| || || ||||| || || || || || ||||| ||
S:      481 CTTGAAGAACCGGATTTTTATAAAACTAAAATCAAGCTCTGCATACTTCTTCATGCTTTC 540

Q:      541 AGAATCAGAGCAGTCACTATAGATAGAGTGATGTCCTACCTGAATGCTTCC 591
            |||||  | ||||| ||||| |||||||||||||  ||| ||||||||||||
S:      541 AGAATTCGGGCAGTGACTATTGATAGAGTGATGAGCTATCTGAATGCTTCC 591
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[0066] In some embodiments, the IL-12sc RNA is encoded by a codon-optimized DNA sequence encoding IL-12sc. In some embodiments, the IL-12sc RNA is encoded by a codon-

optimized DNA sequence encoding IL-12 p40. In some embodiments, the IL-12sc RNA is encoded by a codon-optimized DNA sequence encoding IL-12 p35. In some embodiments, the codon-optimized DNA sequence comprises or consists of SEQ ID NO: 16. In some embodiments, the DNA sequence comprises a codon-optimized DNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 16. In some embodiments, the codon-optimized DNA sequence encoding IL-12 p40 comprises the nucleotides encoding the IL-12sc-p40 (nucleotides 1-984 of SEQ ID NO: 16). In some embodiments, the codon-optimized DNA sequence encoding IL-12 p35 comprises the nucleotides encoding the IL-12sc-p35 (nucleotides 1027-1623 of SEQ ID NO: 16). In some embodiments, the codon-optimized DNA sequence encoding IL-12sc comprises the nucleotides encoding the IL-12sc-p40 (nucleotides 1-984 of SEQ ID NO: 16) and -p35 (nucleotides 1027-1623 of SEQ ID NO: 16) portions of SEQ ID NO: 16 and further comprises nucleotides between the p40 and p35 portions (e.g., nucleotides 985-1026 of SEQ ID NO: 16) encoding a linker polypeptide connecting the p40 and p35 portions. Any linker known to those of skill in the art may be used. The p40 portion may be 5' or 3' to the p35 portion.

[0067] In some embodiments, the IL-12sc RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence encoding IL-12sc. The RNA may also be recombinantly produced. In some embodiments, the RNA sequence is transcribed from a nucleotide sequence comprising SEQ ID NOs: 15 or 16. In some embodiments, the RNA sequence comprises or consists of SEQ ID NOs: 17 or 18. In some embodiments, the RNA sequence comprises or consists of an RNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOs: 17 or 18. In some embodiments, the RNA sequence comprises the nucleotides encoding the IL-12sc-p40 (nucleotides 1-984 of SEQ ID NOs: 17 or 18) and -p35 (nucleotides 1027-1623 of SEQ ID NOs: 17 or 18) portions of SEQ ID NOs: 17 or 18. In some embodiments, the codon-optimized RNA sequence encoding IL-12sc comprises the nucleotides encoding the IL-12sc-p40 (nucleotides 1-984 of SEQ ID NO: 18) and -p35 (nucleotides 1027-1623 of SEQ ID NO: 18) portions of SEQ ID NO: 18 and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide connecting the p40 and p35 portions. Any linker known to those of skill in the art may be used.

[0068] In some embodiments, one or more uridine in the IL-12sc RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine

(m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0069] In some embodiments, the IL-12sc RNA comprises an altered nucleotide at the 5' end. In some embodiments, the RNA comprises a 5' cap. Any 5' cap known in the art may be used. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage including thiophosphate modification. In some embodiments, the 5' cap comprises a 2′-*O* or 3′-*O*-ribose-methylated nucleotide. In some embodiments, the 5' cap comprises a modified guanosine nucleotide or modified adenosine nucleotide. In some embodiments, the 5' cap comprises 7-methylguanylate. In some embodiments, the 5' cap is Cap0 or Cap1. Exemplary cap structures include m7G(5')ppp(5')G, m7,2`*O*-mG(5')ppsp(5')G, m7G(5')ppp(5')2`*O*-mG, and m7,3`*O*-mG(5')ppp(5')2`*O*-mA.

[0070] In some embodiments, the IL-12sc RNA comprises a 5' untranslated region (UTR). In some embodiments, the 5' UTR is upstream of the initiation codon. In some embodiments, the 5' UTR regulates translation of the RNA. In some embodiments, the 5' UTR is a stabilizing sequence. In some embodiments, the 5' UTR increases the half-life of RNA. Any 5' UTR known in the art may be used. In some embodiments, the 5' UTR RNA sequence is transcribed from SEQ ID NOs: 3 or 5. In some embodiments, the 5' UTR RNA sequence comprises or consists of SEQ ID NOs: 4 or 6. In some embodiments, the 5' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOs: 4 or 6.

[0071] In some embodiments, the IL-12sc RNA comprises a 3' UTR. In some embodiments, the 3' UTR follows the translation termination codon. In some embodiments, the 3' UTR regulates polyadenylation, translation efficiency, localization, or stability of the RNA. In some embodiments, the 3' UTR RNA sequence is transcribed from SEQ ID NO: 7. In some embodiments, the 3' UTR RNA sequence comprises or consists of SEQ ID NO: 8. In some embodiments, the 3' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.

[0072] In some embodiments, the IL-12sc RNA comprises both a 5' UTR and a 3' UTR. In some embodiments, the IL-12sc RNA comprises only a 5' UTR. In some embodiments, the IL-12sc RNA comprises only a 3' UTR.

[0073] In some embodiments, the IL-12sc RNA comprises a poly-A tail. In some embodiments, the RNA comprises a poly-A tail of at least about 25, at least about 30, at least about 50 nucleotides, at least about 70 nucleotides, or at least about 100 nucleotides. In some

embodiments, the poly-A tail comprises 200 or more nucleotides. In some embodiments, the poly-A tail comprises or consists of SEQ ID NO: 60.

[0074] In some embodiments, the RNA comprises a 5' cap, a 5' UTR, a nucleic acid encoding IL-12sc, a 3' UTR, and a poly-A tail, in that order.

[0075] In some embodiments, the IL-12sc RNA comprises a DNA sequence comprising or consisting of a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5.

[0076] In some embodiments, the IL-12sc RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IL-12sc RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0077] In some embodiments, the IL-12sc RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[0078] In some embodiments, the IL-12sc RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IL-12sc RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0079] In some embodiments, the IL-12sc RNA comprises a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%,

98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

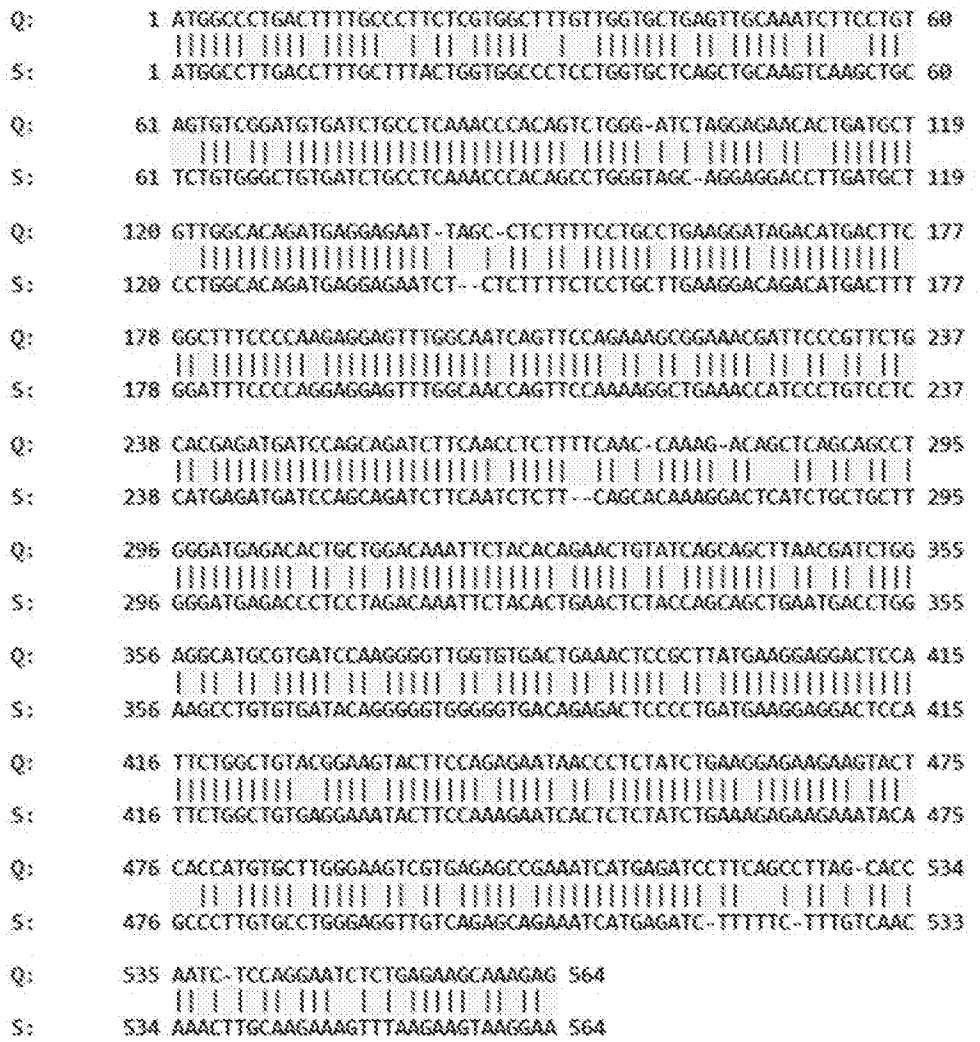
[0080] In some embodiments, the IL-12sc RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 15 or 16; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IL-12sc RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0081] In some embodiments, the IL-12sc RNA comprises an RNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 17 or 18; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 4 or 6; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, one or more uridine in the IL-12sc RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U).

B. Interferon alpha (IFNα)

[0082] In some embodiments, a composition or medical preparation comprising RNA that encodes interferon alpha (IFNα) is provided. In some embodiments, the interferon alpha (IFNα) RNA is encoded by a DNA sequence encoding interferon alpha (IFNα) (e.g., SEQ ID NO: 19). An exemplary DNA sequence encoding this IFNα is provided in SEQ ID NO: 20.

[0083] The alignment of codon optimized IFNα to native IFNα is shown below, where the "S" is native IFNα (NM_000605.3; SEQ ID NO: 20) and the "Q" is codon optimized IFNα (SEQ ID NO: 21). The percent identity is 79%.



[0084] In some embodiments, the IFNα RNA is encoded by a codon-optimized DNA sequence encoding IFNα. In some embodiments, the codon-optimized DNA sequence comprises or consists of the nucleotides of SEQ ID NO: 21. In some embodiments, the DNA sequence comprises or consists of a codon-optimized DNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 21.

[0085] In some embodiments, the IFNα RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence encoding IFNα. The RNA may also be recombinantly produced. In some embodiments, the RNA sequence is transcribed from a nucleotide sequence comprising SEQ ID NOs: 20 or 21. In some embodiments, the RNA sequence comprises or consists of SEQ ID NOs: 22 or 23. In some embodiments, the RNA sequence comprises or consists of an RNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOs: 22 or 23.

[0086] In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, each uridine in the RNA is modified. In some embodiments, each uridine in the RNA is modified with N1-methyl-pseudouridine ($m^1\psi$).

[0087] In some embodiments, the IFNα RNA comprises an altered nucleotide at the 5' end. In some embodiments, the IFNα RNA comprises a 5' cap. Any 5' cap known in the art may be used. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage including thiophosphate modification. In some embodiments, the 5' cap comprises a 2′-*O* or 3′-*O*-ribose-methylated nucleotide. In some embodiments, the 5' cap comprises a modified guanosine nucleotide or modified adenosine nucleotide. In some embodiments, the 5' cap comprises 7-methylguanylate. In some embodiments, the 5' cap is Cap0 or Cap1. Exemplary cap structures include m7G(5')ppp(5')G, m7,2`*O*-mG(5')ppsp(5')G, m7G(5')ppp(5')2`*O*-mG and m7,3`*O*-mG(5')ppp(5')2`*O*-mA.

[0088] In some embodiments, the IFNα RNA comprises a 5' untranslated region (UTR). In some embodiments, the 5' UTR is upstream of the initiation codon. In some embodiments, the 5' UTR regulates translation of the RNA. In some embodiments, the 5' UTR is a stabilizing sequence. In some embodiments, the 5' UTR increases the half-life of RNA. Any 5' UTR known in the art may be used. In some embodiments, the 5' UTR RNA sequence is transcribed from a nucleotide sequence comprising SEQ ID NOs: 3 or 5. In some embodiments, the 5' UTR RNA sequence comprises or consists of SEQ ID NOs: 4 or 6. In some embodiments, the 5' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOs: 4 or 6.

[0089] In some embodiments, the IFNα RNA comprises a 3' UTR. In some embodiments, the 3' UTR follows the translation termination codon. In some embodiments, the 3' UTR regulates polyadenylation, translation efficiency, localization, or stability of the RNA. In some embodiments, the 3' UTR RNA sequence is transcribed from a nucleotide sequence comprising SEQ ID NO: 7. In some embodiments, the 3' UTR RNA sequence comprises or consists of SEQ ID NO: 8. In some embodiments, the 3' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.

[0090] In some embodiments, the IFNα RNA comprises both a 5' UTR and a 3' UTR. In some embodiments, the composition comprises only a 5' UTR. In some embodiments, the composition comprises only a 3' UTR.

[0091] In some embodiments, the IFNα RNA comprises a poly-A tail. In some embodiments, the IFNα RNA comprises a poly-A tail of at least about 25, at least about 30, at least about 50 nucleotides, at least about 70 nucleotides, or at least about 100 nucleotides. In some embodiments, the poly-A tail comprises 200 or more nucleotides. In some embodiments, the poly-A tail comprises or consists of SEQ ID NO: 66.

[0092] In some embodiments, the RNA comprises a 5' cap, a 5' UTR, a nucleic acid encoding IFNα, a 3' UTR, and a poly-A tail, in that order.

[0093] In some embodiments, the IFNα RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5.

[0094] In some embodiments, the IFNα RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0095] In some embodiments, the IFNα RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[0096] In some embodiments, the IFNα RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified

nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[0097] In some embodiments, the IFNα RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 1, 3, or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[0098] In some embodiments, the IFNα RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 20 or 21; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).In some embodiments, the composition comprises an RNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 22 or 23; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 4 or 6; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U).

C. Interleukin 15 (IL-15) sushi

[0099] In some embodiments, a composition or medical preparation comprising RNA that encodes interleukin 15 (IL-15) sushi is provided. As used herein, the term "IL-15 sushi" describes a construct comprising the soluble interleukin 15 (IL-15) receptor alpha sushi domain and mature interleukin alpha (IL-15) as a fusion protein. In some embodiments, the IL-15 sushi RNA is encoded by a DNA sequence encoding IL-15 sushi (SEQ ID NO: 24),

which comprises the soluble IL-15 receptor alpha chain (sushi) followed by a glycine-serine (GS) linker followed by the mature sequence of IL-15. The DNA sequence encoding this IL-15 sushi is provided in SEQ ID NO: 25.

[00100] In some embodiments, the IL-15 sushi RNA is an RNA sequence that is, for example, transcribed from a DNA sequence encoding IL-15 sushi. The RNA may also be recombinantly produced. In some embodiments, the RNA sequence is transcribed from a nucleotide sequence comprising SEQ ID NO: 25. In some embodiments, the nucleotides encoding the linker may be completely absent or replaced in part or in whole with any nucleotides encoding a suitable linker. In some embodiments, the RNA sequence comprises or consists of SEQ ID NO: 26. In some embodiments, the RNA sequence comprises an RNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 26. In some embodiments, the DNA or RNA sequence encoding IL-15 sushi comprises the nucleotides encoding the sushi domain of IL-15 receptor alpha (e.g., nucleotide 1-321 of SEQ ID NOs: 25 or 26) and mature IL-15 (e.g., nucleotide 382-729 of SEQ ID NO: 25 or 26). In some embodiments, the DNA or RNA sequence encoding IL-15 sushi comprises the nucleotides encoding the sushi domain of IL-15 receptor alpha (e.g., nucleotide 1-321 of SEQ ID NOs: 25 or 26) and mature IL-15 (e.g., nucleotide 382-729 of SEQ ID NOs: 25 or 26) and further comprises nucleotides between these portions encoding a linker polypeptide connecting the portions. In some embodiments, the linker comprises nucleotides 322-381 of SEQ ID Nos: 25 or 26. Any linker known to those of skill in the art may be used.

[00101] In some embodiments, one or more uridine in the IL-15 sushi RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00102] In some embodiments, the IL-15 sushi RNA comprises an altered nucleotide at the 5' end. In some embodiments, the IL-15 sushi RNA comprises a 5' cap. Any 5' cap known in the art may be used. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage including thiophosphate modification. In some embodiments, the 5' cap comprises a 2′-*O* or 3′-*O*-ribose-methylated nucleotide. In some embodiments, the 5' cap comprises a modified guanosine nucleotide or modified adenosine nucleotide. In some embodiments, the 5' cap comprises 7-methylguanylate. In some embodiments, the 5' cap is Cap0 or Cap1.

Exemplary cap structures include m7G(5')ppp(5')G, m7,2`*O*-mG(5')ppsp(5')G, m7G(5')ppp(5')2`*O*-mG and m7,3`*O*-mG(5')ppp(5')2`*O*-mA.

[00103] In some embodiments, the IL-15 sushi RNA comprises a 5' untranslated region (UTR). In some embodiments, the 5' UTR is upstream of the initiation codon. In some embodiments, the 5' UTR regulates translation of the RNA. In some embodiments, the 5' UTR is a stabilizing sequence. In some embodiments, the 5' UTR increases the half-life of RNA. Any 5' UTR known in the art may be used. In some embodiments, the 5' UTR RNA sequence is transcribed from SEQ ID NOs: 3 or 5. In some embodiments, the 5' UTR RNA sequence comprises or consists of SEQ ID NOs: 4 or 6. In some embodiments, the 5' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOs: 4 or 6.

[00104] In some embodiments, the IL-15 sushi RNA comprises a 3' UTR. In some embodiments, the 3' UTR follows the translation termination codon. In some embodiments, the 3' UTR regulates polyadenylation, translation efficiency, localization, or stability of the RNA. In some embodiments, the 3' UTR RNA sequence is transcribed from SEQ ID NO: 7. In some embodiments, the 3' UTR RNA sequence comprises or consists of SEQ ID NO: 8. In some embodiments, the 3' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.

[00105] In some embodiments, the IL-15 sushi RNA comprises both a 5' UTR and a 3' UTR. In some embodiments, the IL-15 sushi RNA comprises only a 5' UTR. In some embodiments, the IL-15 sushi RNA comprises only a 3' UTR.

[00106] In some embodiments, the IL-15 sushi RNA comprises a poly-A tail. In some embodiments, the RNA comprises a poly-A tail of at least about 25, at least about 30, at least about 50 nucleotides, at least about 70 nucleotides, or at least about 100 nucleotides. In some embodiments, the poly-A tail comprises 200 or more nucleotides. In some embodiments, the poly-A tail comprises or consists of SEQ ID NO: 66.

[00107] In some embodiments, the RNA comprises a 5' cap, a 5' UTR, a nucleic acid encoding IL-15 sushi, a 3' UTR, and a poly-A tail, in that order.

[00108] In some embodiments, the IL-15 sushi RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5.

[00109] In some embodiments, the IL-15 sushi RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00110] In some embodiments, the IL-15 sushi RNA comprises a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[00111] In some embodiments, the IL-15 sushi RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00112] In some embodiments, the IL-15 sushi RNA comprises a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[00113] In some embodiments, the IL-15 sushi RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 25; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or

100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00114] In some embodiments, the IL-15 sushi RNA comprises an RNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 26; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 4 or 6; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, one or more uridine in the IFNα RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U).

D. Fms Related Tyrosine Kinase 3 Ligand (FLT3-L)

[00115] In some embodiments, a composition or medical preparation comprising RNA that encodes Fms Related Tyrosine Kinase 3 Ligand (FLT3-L) is administered. In some embodiments, the FLT3-L RNA is encoded by a DNA sequence encoding FLT3-L (e.g., SEQ ID NO: 31).

[00116] In some embodiments, the FLT3-L RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence encoding FLT3-L. In some embodiments, the RNA sequence is transcribed from SEQ ID NO: 31. The RNA may also be recombinantly produced. In some embodiments, the RNA sequence comprises or consists of SEQ ID NO: 32. In some embodiments, the RNA sequence comprises an RNA sequence with 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NOs: 32.

[00117] In some embodiments, one or more uridine in the FLT3-L RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$). In some embodiments, the FLT3-L RNA comprises an altered nucleotide at the 5' end. In

some embodiments, the RNA comprises a 5' cap. Any 5' cap known in the art may be used. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage. In some embodiments, the 5' cap comprises a 5' to 5' triphosphate linkage including thiophosphate modification. In some embodiments, the 5' cap comprises a 2′-*O* or 3′-*O*-ribose-methylated nucleotide. In some embodiments, the 5' cap comprises a modified guanosine nucleotide or modified adenosine nucleotide. In some embodiments, the 5' cap comprises 7-methylguanylate. In some embodiments, the 5' cap is Cap0 or Cap1. Exemplary cap structures include m7G(5')ppp(5')G, m7,2`*O*-mG(5')ppsp(5')G, m7G(5')ppp(5')2`*O*-mG and m7,3`*O*-mG(5')ppp(5')2`*O*-mA.

[00118] In some embodiments, the FLT3-L RNA comprises a 5' untranslated region (UTR). In some embodiments, the 5' UTR is upstream of the initiation codon. In some embodiments, the 5' UTR regulates translation of the RNA. In some embodiments, the 5' UTR is a stabilizing sequence. In some embodiments, the 5' UTR increases the half-life of RNA. Any 5' UTR known in the art may be used. In some embodiments, the 5' UTR RNA sequence is transcribed from SEQ ID NOs: 3 or 5. In some embodiments, the 5' UTR RNA sequence comprises or consists of SEQ ID NOs: 4 or 6. In some embodiments, the 5' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NOs: 4 or 6.

[00119] In some embodiments, the FLT3-L RNA comprises a 3' UTR. In some embodiments, the 3' UTR follows the translation termination codon. In some embodiments, the 3' UTR regulates polyadenylation, translation efficiency, localization, or stability of the RNA. In some embodiments, the 3' UTR RNA sequence is transcribed from SEQ ID NO: 7. In some embodiments, the 3' UTR RNA sequence comprises or consists of SEQ ID NO: 8. In some embodiments, the 3' UTR RNA sequence is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8.

[00120] In some embodiments, the FLT3-L RNA comprises both a 5' UTR and a 3' UTR. In some embodiments, the RNA comprises only a 5' UTR. In some embodiments, the composition comprises only a 3' UTR.

[00121] In some embodiments, the FLT3-L RNA comprises a poly-A tail. In some embodiments, the RNA comprises a poly-A tail of at least about 25, at least about 30, at least about 50 nucleotides, at least about 70 nucleotides, or at least about 100 nucleotides. In some embodiments, the poly-A tail comprises 200 or more nucleotides. In some embodiments, the poly-A tail comprises or consists of SEQ ID NO: 66.

[00122] In some embodiments, the FLT3-L RNA comprises a 5' cap, a 5' UTR, nucleotides encoding FLT3-L, a 3' UTR, and a poly-A tail, in that order.

[00123] In some embodiments, the FLT3-L RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5.

[00124] In some embodiments, the FLT3-L RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the FLT3-L RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00125] In some embodiments, the FLT3-L RNA is encoded by a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[00126] In some embodiments, the FLT3-L RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32 and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the FLT3-L RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00127] In some embodiments, the FLT3-L RNA comprises a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 31; at least 70%, 75%, 80%,

85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7.

[00128] In some embodiments, the FLT3-L RNA comprises an RNA sequence that is, for example, transcribed from a DNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 3 or 5; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 7. The RNA may also be recombinantly produced. In some embodiments, one or more uridine in the FLT3-L RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U). In some embodiments, the RNA comprises a modified nucleoside in place of each uridine. In some embodiments, the modified nucleoside is N1-methyl-pseudouridine ($m^1\psi$).

[00129] In some embodiments, the FLT3-L RNA comprises an RNA sequence comprising or consisting of a nucleic acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 32; at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NOs: 4 or 6; and at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 8. In some embodiments, one or more uridine in the FLT3-L RNA is replaced by a modified nucleoside as described herein. In some embodiments, the modified nucleoside replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine ($m^1\psi$) or 5-methyl-uridine (m^5U).

E. Modified RNA

[00130] Each of the RNAs described herein may be modified in any way known to those of skill in the art. In some embodiments, each RNA is modified as follows:

- a modified nucleobase in place of each uridine;
- a Cap1 structure at the 5' end of the RNA.

[00131] In some embodiments, the 5' UTR comprises SEQ ID NOs: 4 or 6. In some embodiments, the RNA has been processed to reduce double-stranded RNA (dsRNA) as described above. The "Cap1" structure may be generated after in-vitro translation by enzymatic capping or during in-vitro translation (co-transcriptional capping).

[00132] In some embodiments, one or more uridine in the RNA is replaced by a modified nucleoside. In some embodiments, the modified nucleoside is a modified uridine.

[00133] In some embodiments, the modified uridine replacing uridine is pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), or 5-methyl-uridine (m5U).

[00134] In some embodiments, one or more cytosine, adenine or guanine in the RNA is replaced by modified nucleobase(s). In one embodiment, the modified nucleobase replacing cytosine is 5-methylcytosine (m^5C). In another embodiment, the modified nucleobase replacing adenine is N^6-methyladenine (m^6A). In another embodiment, any other modified nucleobase known in the art for reducing the immunogenicity of the molecule can be used.

[00135] The modified nucleoside replacing one or more uridine in the RNA may be any one or more of 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridineor 5-bromo-uridine), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 1-ethyl-pseudouridine, 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine (τm^5U), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine(τm5s2U), 1-taurinomethyl-4-thio-pseudouridine), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α-thio-uridine, 2′-O-methyl-uridine (Um), 5,2′-O-dimethyl-uridine (m^5Um), 2′-O-methyl-pseudouridine (ψm), 2-thio-2′-O-

methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2′-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2′-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2′-O-methyl-uridine ($cmnm^5$Um), 3,2′-O-dimethyl-uridine (m^3Um), 5-(isopentenylaminomethyl)-2′-O-methyl-uridine (inm^5Um), 1-thio-uridine, deoxythymidine, 2′-F-ara-uridine, 2′-F-uridine, 2′-OH-ara-uridine, 5-(2-carbomethoxyvinyl) uridine, 5-[3-(1-E-propenylamino)uridine, or any other modified uridine known in the art.

3. Therapeutic Methods

[00136] The compositions and medical preparations provided herein may be used in methods, e.g., therapeutic methods. In some embodiments, the compositions, medical preparations, and RNA are administered to humans.

[00137] In some embodiments, the invention comprises the use of a composition or medical preparation in therapeutic methods, wherein the therapeutic method is for treating solid tumors, and wherein the composition or medical preparation comprises RNA, wherein the RNA consists of RNA encoding IFNα, RNA encoding IL-15 sushi, RNA encoding IL-12sc, and RNA encoding FLT3-L.

[00138] In some embodiments, the invention comprises the use of a composition or medical preparation in therapeutic methods, wherein the therapeutic method is for treating solid tumors, and wherein the composition or medical preparation comprises RNA, wherein the RNA consists of RNA encoding IFNα, RNA encoding IL-15 sushi, and RNA encoding IL-12sc.

[00139] In some embodiments, the composition or medical preparation for use in therapeutic methods comprises RNA encoding IL-12sc protein and further comprising RNA selected from RNA encoding IFNα protein and RNA encoding IL-15 sushi protein.

[00140] In some embodiments, the composition or medical preparation for use in therapeutic methods comprises RNA encoding IL-15 sushi and further comprising RNA encoding IFNα protein and RNA encoding IL-12sc protein.

[00141] In some embodiments, the composition or medical preparation for use in therapeutic methods comprises RNA encoding IFNα protein and further comprising RNA encoding IL-12sc and RNA encoding IL-15 sushi.

[00142] In some embodiments, the composition or medical preparation for use in therapeutic methods comprises RNA encoding FLT3-L and one or more of RNA encoding IL-12sc, RNA encoding IL-15 sushi, and RNA encoding IFNα.

[00143] In some embodiments, the medical preparation or composition described herein is for pharmaceutical use. In some embodiments, the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder. In some instances, the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing a solid tumor.

[00144] In some embodiments, the solid tumor is a sarcoma, carcinoma, or lymphoma.

[00145] In some instances, the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.

[00146] In some embodiments, the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.

[00147] In some embodiments, the RNAs are administered as a 1:1:1, or 1:1:1:1 ratio based on equal RNA mass. For example, 20 μg of IL-15-sushi, 20 μg of IL-12sc, 20 μg of IFNα and optionally 20 μg FLT3-L.

[00148] In some embodiments, the medical preparation or composition described herein is for pharmaceutical use and is administered to a subject with another therapy. In some embodiments, the other therapy is an anti-PD1 antibody, an anti-CTLA4 antibody, or a combination of an anti-PD1 antibody and anti-CTLA4 antibody.

[00149] In some embodiments, the anti-PD1 antibody is a chimeric, humanized or human antibody. In some embodiments, the anti-PD-1 antibody is isolated and/or recombinant. Examples of anti-PD-1 antibodies are nivolumab, pembrolizumab, cemiplimab, MEDI0608 (formerly AMP-514; see, e.g., WO 2012/145493 and U.S. Patent No. 9,205,148), PDR001 (see, e.g., WO 2015/112900), PF-06801591 (see, e.g., WO 2016/092419), BGB-A317 (see, e.g., WO 2015/035606).

[00150] In some embodiments, the anti-PD-1 antibody is one of those disclosed in WO 2015/112800 (such as those referred to as H1M7789N, H1M7799N, H1M7800N, H2M7780N, H2M7788N, H2M7790N, H2M7791N, H2M7794N, H2M7795N, H2M7796N, H2M7798N, H4H9019P, H4xH9034P2, H4xH9035P2, H4xH9037P2, H4xH9045P2, H4xH9048P2, H4H9057P2, H4H9068P2, H4xH9119P2, H4xH9120P2, H4xH9128P2,

H4xH9135P2, H4xH9145P2, H4xH8992P, H4xH8999P and H4xH9008P in Table 1 of the PCT publication, and those referred to as H4H7798N, H4H7795N2, H4H9008P and H4H9048P2 in Table 3 of the PCT publication). The disclosure of WO 2015/112800 is incorporated by reference herein in its entirety. For example, the antibodies disclosed in WO 2015/112800 and related antibodies, including antibodies and antigen-binding fragments having the CDRs, VH and VL sequences, or heavy and light chain sequences disclosed in that PCT publication, as well as antibodies and antigen-binding fragments binding to the same PD-1 epitope as the antibodies disclosed in that PCT publication, can be used in conjunction with the RNA compositions of the present invention to treat and/or prevent cancer.

[00151] In some embodiments, the anti-PD-1 antibody may comprise the heavy and light chain amino acid sequences shown below as SEQ ID NOs: 79 and 80, respectively; the VH and VL sequences in SEQ ID NOs: 87 and 88 (shown in italics), or one or more (e.g., all six) CDRs in SEQ ID NOs: 79 and 80 (shown in bold boxes). In some embodiments, an antibody comprising the following CDRs is encompassed:

HCDR1 = GFTFSNFG (SEQ ID NO: 81)
HCDR2 = ISGGGRDT (SEQ ID NO: 82)
HCDR3 = VKWGNIYFDY (SEQ ID NO: 83)
LCDR1 = LSINTF (SEQ ID NO: 84)
LCDR2 = AAS (SEQ ID NO: 85)
LCDR3 = QQSSNTPFT (SEQ ID NO: 86).

[00152] An exemplary antibody comprising a heavy chain comprising the VH and VL sequences in SEQ ID NOs: 87 and 88 (shown in italics) is the fully human anti-PD-1 antibody known as REGN2810 (cemiplimab).

[00153] Anti-PD-1 Mab heavy chain

*EVQLLESGGV LVQPGGSLRL SCAAS**GFTFS NFG**MTWVRQA PGKGLEWVSG **ISGGGRDT**YF*
*ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYC**VKWG NIYFDY**WGQG TLVTVSS*AST
KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY
SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF
PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV
SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV
SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF
SCSVMHEALH NHYTQKSLSL SLGK (SEQ ID NO:79)

HCDR1 = GFTFSNFG (SEQ ID NO: 81)
HCDR2 = ISGGGRDT (SEQ ID NO: 82)
HCDR3 = VKWGNIYFDY (SEQ ID NO: 83)

[00154] Anti-PD-1 Mab light chain

*DIQMTQSPSS LSASVGDSIT ITCRAS**LSIN TF**LNWYQQKP GKAPNLLIY**A AS**SLHGGVPS*
*RFSGSGSGTD FTLTIRTLQP EDFATYYC**QQ SSNTPFT**FGP GTVVDFR*RTV AAPSVFIFPP
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC (SEQ ID NO:80)

LCDR1 = LSINTF (SEQ ID NO: 84)
LCDR2 = AAS (SEQ ID NO: 85)
LCDR3 = QQ SSNTPFT (SEQ ID NO: 86)

[00155] In some embodiments, the RNAs may be delivered via injection into the tumor (e.g., intratumorally), near the tumor (peri-tumorally), or near the site of a tumor removal, and the antibody may be delivered in the same manner or systemically, such as, for example, enteral or parenteral, including, via injection, infusion, and implantation. Administration may be simultaneous or sequential. If sequential, administration can be in any order and at any appropriate time interval known to those of skill in the art.

[00156] In some embodiments, therapeutic RNA compositions are delivered directly into the tumor, or near the tumor or the site of tumor removal together with another therapy. In some embodiments, therapeutic RNA compositions are delivered directly into the tumor, or near the tumor or site of tumor removal while another agent is delivered systemically.

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[00157] This description and exemplary embodiments should not be taken as limiting. For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing quantities, percentages, or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about," to the extent they are not already so modified. "About" indicates a degree of variation that does not substantially affect the properties of the described subject matter, e.g., within 10%, 5%, 2%, or 1%. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[00158] It is noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the," and any singular use of any word, include plural referents unless expressly and unequivocally limited to one referent. As used herein, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of

items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

EXAMPLES

[00159] The following examples are provided to illustrate certain disclosed embodiments and are not to be construed as limiting the scope of this disclosure in any way.

Example 1 –Materials and Methods

[00160] **B16F10 tumor model**: Female C57BL/6J mice (Jackson Laboratory; Bar Harbor, ME), 6-8 weeks-old and weighing between 17.0 and 20.9 g were acclimated for at least three days prior to study enrollment. Mice had free access to food (Harlan 2916 rodent diet, Massachusetts, USA) and sterile water and housed on 12 hours light/dark cycle at 22°C ± 2°C with a relative humidity of 55% ± 15%. B16F10 cells were obtained from the American Type Culture Collection (ATCC) (Manassas, Virginia USA) (Cat No. CRL-6475) and cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Life technologies, Cat No. 11995) supplemented with 10% heat inactivated Fetal Bovine Serum (HI FBS) (Life technologies, Cat No. 10082-147) in 5% CO2 at 37°C. The cells were harvested using 0.25% Trypsin-EDTA (Life technologies, Cat No. 25200-056), resuspended in Dulbecco's phosphate-buffered saline (DPBS) (Life technologies, Cat No. 14190-144), and 0.5 x 10^6 cells/200 µl per mouse subcutaneously (SC) implanted into the right flank of female C57BL/6J mice.

[00161] **Tumor monitoring:** B16F10 tumors were measured with a caliper twice weekly until final sacrifice. When a tumor size reached approximately 2000 mm^3 or there were animal health issues (20% area of a tumor ulcerated), animals were euthanized. Tumor regression was defined as i) tumor volume < 20 mm3 at the end of the study or ii) $T^F/T^0 < 1$, where the T^F equals the final tumor volume and T^0 equals tumor volume on the day of the first intratumoral RNA injection.

[00162] **CT26 tumor model**: For studies utilizing the CT26 tumor model, female Balb/c Rj mice (Janvier, Genest-St.-Îsle, France), 6-8 weeks of age, with a weight between 17 and 24 g, were acclimated for at least six days prior to study enrollment. Mice had free access to food (ssniff M-Z autoclavable Soest, Germany) and sterile water and housed on 12 hours light/dark cycle at 22°C ± 2°C with a relative humidity of 55% ± 10%. CT26 cells were obtained from the (ATCC® CRL-2638™) and cultured in Roswell Park Memorial Institute medium (RPMI) 1640 Medium, GlutaMAX™ (Life technologies, Cat No. 61870-044) supplemented with 10% Fetal Bovine Serum (FBS) (Biochrom, Cat No. S 0115) in 5% CO2

at 37°C. The cells were harvested using StemPro® Accutase® Cell Dissociation Reagent (Life technologies, Cat No. A1110501), resuspended in DPBS (Life technologies, Cat No. 14190-169), and 0.5 x 10^6 cells/100 µl per mouse SC implanted into the right shaven flank of female Balb/c Rj mice. Intratumoral RNA injections were initiated 11-15 days after inoculation of the tumors. Tumor growth in the CT26 tumor model was assessed by caliper measurements every 2-3 days and is expressed as the product of the perpendicular diameters using the following formula: a2*b/2 where b is the longer of the two diameters (a<b).

[00163] **Gp70-reactive CD8+ cells**: In addition to tumor growth, gp70-reactive CD8+ T-cells were measured in blood where indicated. Blood samples were taken using EDTA-coated tubes. 100 µL of blood was transferred to FACS tubes and antibody mixture was added containing T-Select H-2Ld MuLV gp70 Tetramer-SPSYVYHQF-APC (MBL (TS-M-521-2), 4 µL for 100 µL blood), anti-CD8a FITC (life technologies (MCD801), 1 µL for 100 µL blood)) and anti-CD45 V500 (BD (561487), 1 µL for 100 µL blood)). After 20 min incubation at room temperature Blood Lysis Buffer (BD (349202), 300 µL per tube) was added and incubated for further 6 min. Then samples were washed twice with PBS-EDTA buffer. FACS samples were analyzed on a FACS Canto II flow cytometer.

[00164] **RNA modification**: Unless stated otherwise, all RNA was modified as follows. Synthetic DNA fragments coding for the gene of interest were cloned into a common starting vector, comprising a 5'-UTR (corresponding in some cases to the Tobacco Etch Viral leader sequences TEV, SEQ ID NO: 3), a 3' UTR consisting of two elements called F and I (corresponding is some cases to SEQ ID NO: 7), and a poly(A)-tail of 110 nucleotides in total (A30-Linker-A70 structure; SEQ ID NO: 60). Linearization of plasmid DNA was performed downstream of the poly(dA:dT) with a class IIS restriction enzyme to generate a template with no additional nucleotide beyond the poly(dA:dT) (*see* Holtkamp et al., *Blood* 108(13):4009-172006 (2006)). Linearized plasmid DNA was subjected to in vitro transcription with T7 RNA polymerase (Thermo Fisher) as previously described (*see* Grudzien-Nogalska E et al., *Methods Mol Biol.* 969:55-72 (2013)) in the presence of 7.5 mM ATP, CTP, GTP, and N1-methyl-pseudouridinetriphosphate. RNA was then purified using magnetic particles (*Berensmeier 2006*), and subsequently Cap1 structure was enzymatically introduced using a commercially available system based on the Vaccinia virus capping enzyme (NEB) and addition of RNA Cap 2'-O-methyltransferase (NEB). Afterwards, the RNA was subjected to a further purification procedure by Cellulose-based chromatography to remove double-stranded RNA impurities (see Day PR et al, *Phytopathology* 67:1393 (1977); Morris TJ et al., *Phytopathology* 69:854-858 (1979); and Castillo A et al., *Virol J.* 8:38

(2011)). RNA concentration and quality were assessed spectrophotometry and analyzed by capillary gel electrophoresis systems, respectively. Presence of dsRNA was assessed in a Northwestern dot-blot assay using dsRNA-specific J2 mAb (English & Scientific Consulting) as described in Karikó et al. *Nucleic Acids Res.* 39(21):e142 (2011).

[00165] **Preparation of RNA for in vivo studies:** The respective RNA mixtures were prepared for in vivo studies by mixing equal quantities (micrograms) of RNA in water at 2X the intended dose. RNAs injected into mice were the mouse versions of the RNAs described in Table 1 except for FLT3-L, where SEQ ID NO: 65 was used (human FLT3-L with murine optimized secretion sequence). In some instances, the RNA mixture was frozen at -80C until the day of intratumoral injection. On the day of injection, RNA was thawed and mixed with an equal volume of 2X sterile Ringer's solution. In other instances, the RNA mixture was freshly prepared and diluted in Ringer solution to a final concentration of 1X RNA/Ringer solution. In both instances, the resulting 1X RNA/Ringer solution was used for intratumoral injection.

Example 2 –Combination of three RNAs reduce tumor volume in vivo

We previously tested the effect of a cytokine RNA mixture comprising different combinations of three RNAs in CT26 tumor bearing mice as described above. Tumors treated with four injections of RNA (10 µg RNA/target) encoding IL-15 sushi, IL-12sc, GM-CSF and IFNα induced regression in 10 of 10 treated tumors (FIG 1A; Table 2 (Tables and Figures represent the same data; tables provide raw data)). Tumors treated with the 3-combination RNA mixtures of i) IL-15 sushi, IL-12sc and IFNα (no GM-CSF), ii) IL-15 sushi, GM-CSF and IFNα (no IL-12sc), iii) IL-12sc, GM-CSF and IFNα (no IL-15 sushi), and iv) IL-15 sushi, IL-12sc, and GM-CSF (no IFNα) resulted in regression of 8 out of 10 (IL-15 sushi, IL-12sc and IFNα (no GM-CSF; FIG 1B; Table 3), 6 out of 10 (IL-15 sushi, GM-CSF and IFNα (no IL-12sc; FIG 1C; Table 4), 8 out of 10 (IL-12sc, GM-CSF and IFNα (no IL-15 sushi; FIG 1D; Table 5), 7 out of 10 (IL-15 sushi, IL-12sc, and GM-CSF (no IFNα; FIG 1E; Table 6). No tumors treated with control RNA (40 µg RNA injected at each treatment) displayed tumor regression (FIG 1F; Table 7). To analyze tumor growth kinetics, mean tumor volumes were calculated for each treatment group up to day 33 (FIG 1G). Tumor growth repression T/C (Tumor/Control based on mean tumor volume) was plotted to day 19 (FIG 1H) for each of the treatment groups.

[00166] Table 2 (corresponding to FIG 1A). Values = tumor size mm^3

day	Animal: 1	2	3	4	5	6	7	8	9	10
11	18	18	40	13.5	32	18	13.5	32	32	40
13	32	18	32	18	32	18	18	18	32	32
16	32	13.5	6	13.5	32	18	32	32	32	6
19	13.5	4	4	4	32	6	13.5	13.5	13.5	4
22	13.5	4	1	4	32	6	6	13.5	6	4
26	6	4	1	4	18	4	6	6	4	4
29	4	4	1	1	18	1	6	4	0	4
33	4	4	0	0	6	0	4	4	0	4

[00167] Table 3 (corresponding to FIG 1B). Values = tumor size mm^3

day	Animal 1	2	3	4	5	6	7	8	9	10
11	18	32	18	40	13.5	18	18	40	32	18
13	18	32	40	40	13.5	18	13.5	40	62.5	18
16	18	13.5	22.5	40	13.5	13.5	6	108	171.5	13.5
19	6	6	18	32	6	13.5	4	108	196	4
22	13.5	6	18	18	4	13.5	4	171.5	405	4
26	6	4	6	6	4	6	4	288	405	1
29	4	1	6	4	1	6	1	600	567	1
33	0	0	4	0	0	4	0	1352	1152	0

[00168] Table 4 (corresponding to FIG 1C). Values = tumor size mm^3

day	Animal 1	2	3	4	5	6	7	8	9	10
11	40	32	18	13.5	32	40	13.5	18	18	18
13	62.5	32	18	13.5	40	40	13.5	18	13.5	40
16	196	32	32	18	62.5	75	13.5	18	6	75
19	405	18	32	13.5	40	75	6	13.5	4	75
22	726	13.5	40	6	62.5	196	6	13.5	1	108
26	1470	4	48	4	32	288	4	9	1	126
29	1800	4	126	1	6	550	1	1	0	196
33		0	196	0	4	1470	0	0	0	288

[00169] Table 5 (corresponding to FIG 1D). Values = tumor size mm^3

day	Animal 1	2	3	4	5	6	7	8	9	10
11	13.5	18	32	32	40	18	32	40	18	13.5
13	13.5	32	32	32	40	18	32	32	13.5	13.5
16	4	32	32	32	62.5	13.5	18	18	13.5	40
19	4	13.5	13.5	13.5	75	6	13.5	13.5	18	126
22	4	18	13.5	18	108	6	13.5	13.5	18	600
26	1	6	13.5	13.5	126	4	6	4	13.5	1028.5
29	1	4	4	4	108	4	4	4	6	1764

33	0	1	4	4	75	1	1	1	1	1764

[00170] Table 6 (corresponding to FIG 1E). Values = tumor size mm^3

day	Animal 1	2	3	4	5	6	7	8	9	10
11	13.5	13.5	32	32	40	32	18	18	18	40
13	13.5	13.5	32	18	62.5	40	32	18	40	40
16	6	6	18	13.5	75	108	32	40	126	40
19	4	4	13.5	6	126	126	40	40	196	40
22	4	1	6	4	126	171.5	32	32	256	32
26	4	1	6	4	108	171.5	18	32	288	18
29	1	0	1	1	87.5	196	6	6	320	6
33	0	0	0	0	40	162	4	1	352	4

[00171] Table 7 (corresponding to FIG 1F). Values = tumor size mm^3

day	Animal 1	2	3	4	5	6	7	8	9	10
11	32	13.5	40	40	18	18	13.5	18	18	40
13	40	13.5	48	108	18	18	32	32	32	75
16	40	18	126	196	18	75	126	32	108	62.5
19	75	75	196	288	18	108	220.5	62.5	220.5	62.5
22	171.5	288	288	500	75	288	486	108	352	62.5
26	288	726	550	936	171.5	500	907.5	144	907.5	62.5
29	665.5	1568	1372	1568	364.5	1372	1764	288	1296	256
33	1470				1372			1372		1470

[00172] In a separate experiment using the B16F10 tumor model, anti-tumor activity of the 4-combination RNA mixture of IL-15 sushi, IL-12sc, GM-CSF and IFNα was compared to the 3-combination mixture of IL-15 sushi, IL-12sc, and IFNα. Mice received a single RNA injection intratumorally on day 11. Treatment with the 4-combination cytokine RNA mixture that encoded IL-15 sushi, IL-12sc, GM-CSF and IFNα resulted in tumor regression in 6 out of 10 mice (FIG 2A). Tumors treated with the 3-combination RNA mixture of IL-15 sushi, IL-12sc, and IFNα (no GM-CSF) had tumor regression in 8 out of 10 mice (FIG 2B), while no tumor regression was noted for mice treated with control RNA encoding luciferase (FIG 2C).

Example 3 –Combination of four RNAs reduce tumor volume and promotes immune responses in vivo

[00173] A 4-cytokine mixture of RNAs encoding IL-15 sushi, IL-12sc, IFNα, and FLT3-L was injected into CT26 tumor bearing mice on days 13, 16, 20 and 24 and tumor growth was monitored to day 50 (5 μg RNA/target and 20 μg of control RNA). As shown in

Figure 3, intratumoral injection of a combination of four RNAs encoding IL-15 sushi, IL-12sc, IFNα, and FLT3-L induced tumor regression in 4 out of the 10 mice (FIG 3A), while mice treated with a control RNA encoding luciferase displayed tumor regression in 1 of 10 animals (FIG 3B). These data were confirmed in a repeat study of similar design. In the repeat experiment, a mixture of cytokine RNA encoding IL-15 sushi, IL-12sc, IFNα, and FLT3-L (5 μg RNA/target and 20 μg of control RNA injected on days 11, 14, 17 and 21) led to tumor regression in 9 of 11 mice (FIG 3C), while treatment with control RNA encoding luciferase displayed tumor regression in 1 of 11 mice (FIG 3D). Mice treated with a mixture of cytokine RNA encoding IL-15 sushi, IL-12sc, IFNα, and GM-CSF displayed tumor regression in 2 of 10 animals (FIG 3E).

[00174] In a separate experiment utilizing the B16F10 tumor model, a mixture of RNAs encoding IL-15 sushi, IL-12sc, IFNα, and GM-CSF (FIG 4A); IL-15 sushi, IL-12sc, IFNα, and FLT3-L (FIG 4B); or control RNA encoding luciferase (FIG 4C) (2 μg RNA/target and 8 μg of control RNA) was injected once into B16F10 tumor bearing mice on day 11 and tumor growth was monitored to day 57. As shown in Figure 4, intratumoral injection of a combination of four RNAs encoding IL-15 sushi, IL-12sc, IFNα, and GM-CSF induced tumor regression in 7 out of the 10 mice (FIG 4A), intratumoral injection of a combination of four RNAs encoding IL-15 sushi, IL-12sc, IFNα, and FLT3-L induced tumor regression in 6 out of the 10 mice (FIG 4B), while mice treated with a control RNA encoding luciferase displayed tumor regression in 0 of 10 animals (FIG 4C).

[00175] B16F10 tumor bearing mice received single injection of RNA (2 μg RNA/target or 8 μg of control RNA) and 7 days following intratumoral injection the tumors were removed, dissociated and stained with a panel of antibodies to assess intratumoral immune populations. The number of CD8+ T cells and NK cells were enumerated for the different treatment groups. Results are shown in FIGs 5A and 5B.

[00176] Mice bearing a single CT26 tumor received four intratumoral injections of a cytokine RNA mixture of 1) IL-15 sushi, GM-CSF, IFNα, and IL-12sc; 2) IL-15 sushi, FLT3L, IFNα, and IL-12sc; or 3) control RNA encoding luciferase on days 13, 16, 20, 24 (5 μg RNA/target per injection and 20 μg RNA per control injection). Blood was collected 19 and 31 days after first intratumoral RNA administration and T cells specific for the gp70 tumor antigen were quantified by flow cytometry. Frequency of T cells specific for the gp70 tumor antigen in blood were strongly increased in mice upon intratumoral injection of RNA cytokines compared to mice that had received control RNA (FIGs. 6A (day 19) and 6B (day 31)). On day 31, frequencies of gp70-specifc T cells were higher for the FLT3L containing

mixture compared to the GM-CSF containing mixture (FIG 6B). In a separate experiment, a mixture of cytokine RNA IL-15 sushi, IL-12sc, IFNα, and FLT3-L led to strongly increased frequency of gp70-specifc T cells compared to control RNA on day 24 (FIG 6C).

We claim:

1. A composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein.
2. The medical preparation or composition according to claim 1, further comprising RNA encoding an FLT3-L protein.
3. The composition according to claim 1 or claim 2.
4. The medical preparation according to claim 1 or claim 2.
5. The medical preparation or composition of any one of claims 1-4, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and wherein the ratio is validated by quantitative RT-PCR.
6. The medical preparation or composition of any one of claims 1-5, wherein the RNA integrity is greater than or equal to 70%.
7. The medical preparation or composition of any one of claims 1-6, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.
8. The medical preparation or composition of any one of claims 1-7, wherein the IFNα protein is an IFNα2b protein.
9. The medical preparation or composition of any one of claims 1-8, wherein
   (i) the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18; and/or
   (ii) the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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:14; and/or
   (iii) the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.
10. The medical preparation or composition of any one of claims 1-9, wherein

(i) the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26; and/or

(ii) the IL-15 sushi protein 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; and/or

(iii) the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

11. The medical preparation or composition of any one of claims 1-10, wherein

(i) the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or

(ii) the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

12. The medical preparation or composition of any one of claims 2-11, wherein

(i) the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

(ii) the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

13. The medical preparation or composition of any one of claims 1-12, wherein at least one RNA comprises a modified nucleoside in place of at least one uridine.

14. The medical preparation or composition of any one of claims 1-13, wherein at least one RNA comprises a modified nucleoside in place of each uridine.

15. The medical preparation or composition of any one of claims 1-14, wherein each RNA comprises a modified nucleoside in place of at least one uridine.
16. The medical preparation or composition of any one of claims 1-15, wherein each RNA comprises a modified nucleoside in place of each uridine.
17. The medical preparation or composition of any one of claims 13-16, wherein the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).
18. The medical preparation or composition of any one of claims 13-17, wherein at least one RNA comprises more than one type of modified nucleoside, wherein the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).
19. The medical preparation or composition of claim 18, wherein the modified nucleoside is N1-methyl-pseudouridine (m1ψ).
20. The medical preparation or composition of claims 1-19, wherein at least one RNA comprises the 5' cap $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG or 3′-O-Me-m^7G(5')ppp(5')G.
21. The medical preparation or composition of claims 1-20, wherein each RNA comprises the 5' cap $m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG or 3′-O-Me-m^7G(5')ppp(5')G.
22. The medical preparation or composition of claims 1-21, wherein at least one RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.
23. The medical preparation or composition of any one of claims 1-22, wherein each RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.
24. The medical preparation or composition of any one of claims 1-23, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.
25. The medical preparation or composition of any one of claims 1-24, wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

26. The medical preparation or composition of any one of the preceding claims, wherein at least one RNA comprises a poly-A tail.
27. The medical preparation or composition of any one of claims 1-25, wherein each RNA comprises a poly-A tail.
28. The medical preparation or composition of claim 26 or 27, wherein the poly-A tail comprises at least 100 nucleotides.
29. The medical preparation or composition of any one of claims 26-28, wherein the poly-A tail comprises the poly-A tail shown in SEQ ID NO: 66.
30. The medical preparation or composition of any one of claims 1-29wherein one or more RNA comprises:
    a. a 5' cap comprising $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$ or 3′-O-Me-m^7G(5')ppp(5')G;
    b. a 5' UTR comprising (i) a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6;
    c. a 3' UTR comprising (i) the nucleotide sequence of SEQ ID NO: 8, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO:8; and
    d. a poly-A tail comprising at least 100 nucleotides.
31. The medical preparation or composition of claim 30, wherein the poly-A tail comprises SEQ ID NO: 66.
32. The medical preparation or composition of any one of claims 1-31, which is a pharmaceutical composition comprising the RNAs.
33. The medical preparation or composition of claim 32, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.
34. The medical preparation or composition of any one of claims 1-33, wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof.
35. The medical preparation or composition of any one of claims 1-34for pharmaceutical use.
36. The medical preparation or composition of claim 35, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

37. The medical preparation or composition of claim 36, wherein the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing a solid tumor.
38. The medical preparation or composition of claim 37, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.
39. The medical preparation or composition of any one of claims 37 or 38, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.
40. The medical preparation or composition of any one of claims 37-39, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.
41. The medical preparation or composition of any one of claims 1-40, wherein the RNA is for intra-tumoral or peri-tumoral administration.
42. The medical preparation or composition of any one of claims 1-41, wherein the RNA is formulated for injection.
43. The medical preparation or composition of any one of claims 1-42, wherein the RNA is for administration to a human.
44. The medical preparation or composition of any one of claims 37-43, wherein treating or preventing the solid tumor comprises reducing the size of a tumor, preventing the reoccurrence of cancer in remission, or preventing cancer metastasis in a subject.
45. The medical preparation or composition of any one of claims 36-44, wherein the therapeutic or prophylactic treatment of a disease or disorder further comprises administering a further therapy.
46. The medical preparation or composition of claim 45, wherein the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) immunotherapy, (iii) radiotherapy, and (iv) chemotherapy.

47. The medical preparation or composition of any one of claims 45-46, wherein the further therapy comprises administering a further therapeutic agent.
48. The medical preparation or composition of claim 47, wherein the further therapeutic agent is an anti-cancer therapeutic agent.
49. The medical preparation or composition of claim 47 or 48, wherein the further therapeutic agent is a checkpoint modulator.
50. The medical preparation or composition of claim 49 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.
51. A method for treating or reducing the likelihood of a solid tumor comprising administering to a subject in need thereof a first RNA, wherein the first RNA encodes an IL-12sc protein, an IL-15 sushi protein, an FLT3-L protein, or an IFNα protein and the subject is further treated with additional RNA, wherein:
    a. if the first RNA encodes an IL-12sc protein, then the additional RNA comprises RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, RNA encoding and a FLT3-L protein; or
    b. if the first RNA encodes an IL-15 sushi protein, then the additional RNA comprises RNA encoding an IL-12sc protein, RNA encoding an IFNα protein, and RNA encoding a FLT3-L protein; or
    c. if the first RNA encodes an IFNα protein, then the additional RNA comprises RNA encoding an IL-15 sushi protein, RNA encoding an IL-12sc protein, and RNA encoding a FLT3-L protein; or
    d. if the first RNA encodes a FLT3-L protein, then the additional RNA comprises RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding an IL-12sc protein; or
    e. if the first RNA encodes an IL-12sc protein, then the additional RNA comprises RNA encoding an IL-15 sushi protein and RNA encoding an IFNα protein; or
    f. if the first RNA encodes an IL-15 sushi protein, then the additional RNA comprises RNA encoding an IL-12sc protein and RNA encoding an IFNα protein; or
    g. if the first RNA encodes an IFNα protein, then the additional RNA comprises RNA encoding an IL-15 sushi protein and RNA encoding an IL-12sc protein.
52. A kit comprising the composition of any one of claims 1-50.

53. The medical preparation of any one of claims 1-2 or 4-50, wherein the medical preparation is a kit.
54. The medical preparation of claim 53 or the kit of claim 52, wherein the RNAs are in separate vials.
55. The kit of any one of claims 52-54, further comprising instructions for use of the composition for treating or preventing a solid tumor.
56. RNA for use in a method for treating or preventing a solid tumor in a subject, wherein the method comprises administering RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein.
57. Use of RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, and RNA encoding an IFNα protein for the treatment of solid tumor.
58. The RNA or use of any one of claims 56-57, further comprising RNA encoding an FLT3-L protein.
59. The RNA or use of any one of claims 56-58, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and wherein the ratio is validated by quantitative RT-PCR.
60. The RNA or use of any one of claims 56-59, wherein the RNA integrity is greater than or equal to 70%.
61. The RNA or use of any one of claims 56-60, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.
62. The RNA or use of any one of claims 56-61, wherein the IFNα protein is an IFNα2b protein.
63. The RNA or use of any one of claims 56-62, wherein
    (i) the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18 and/or
    (ii) the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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: 14; and/or
    (iii) the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further

comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

64. The RNA or use of any one of claims 56-63, wherein

(i) the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26 and/or

(ii) the IL-15 sushi protein 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; and/or

(iii) the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

65. The RNA or use of any one of claims 58-64, wherein

(i) the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

(ii) the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

66. The RNA or use of any one of claims 56-65, wherein

(i) the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or

(ii) the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

67. The RNA or use of any one of claims 56-66, wherein at least one RNA comprises a modified nucleoside in place of at least one uridine.
68. The RNA or use of any one of claims 56-67, wherein at least one RNA comprises a modified nucleoside in place of each uridine.
69. The RNA or use of any one of claims 56-68, wherein each RNA comprises a modified nucleoside in place of at least one uridine.
70. The RNA or use of any one of claims 56-69, wherein each RNA comprises a modified nucleoside in place of each uridine.
71. The RNA or use of any one of claims 67-70, wherein the modified nucleoside is independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ) and 5-methyl-uridine (m5U).
72. The RNA of any one of claims 67-71, wherein at least one RNA comprises more than one type of modified nucleoside, wherein the modified nucleosides are independently selected from pseudouridine (ψ), N1-methyl-pseudouridine (m1ψ), and 5-methyl-uridine (m5U).
73. The RNA or use of claim 72, wherein the modified nucleoside is N1-methyl-pseudouridine (m1ψ).
74. The RNA or use of any one of claims 56-73, wherein at least one RNA comprises the 5' cap m27,3'-OGppp(m12'-O)ApG or 3′-O-Me-m7G(5')ppp(5')G.
75. The RNA or use of any one of claims 56-73, wherein at each RNA comprises the 5' cap m27,3'-OGppp(m12'-O)ApG or 3′-O-Me-m7G(5')ppp(5')G.
76. The RNA or use of any one of claims 56-75, wherein at least one RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.
77. The RNA or use of any one of claims 56-76, wherein each RNA comprises a 5' UTR comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6.
78. The RNA or use of any one of claims 56-77, wherein at least one RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.

79. The RNA or use of any one of claims 56-78, wherein each RNA comprises a 3' UTR comprising the nucleotide sequence of SEQ ID NO: 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: 8.
80. The RNA or use of any one of claims 56-79, wherein at least one RNA comprises a poly-A tail.
81. The RNA or use of any one of claims 56-80, wherein each RNA comprises a poly-A tail.
82. The RNA or use of claim 80 or 81, wherein the poly-A tail comprises at least 100 nucleotides.
83. The RNA or use of any one of claims 80-82, wherein the poly-A tail comprises the poly-A tail shown in SEQ ID NO: 66.
84. The RNA or use of any one of claims 56-83, wherein one or more RNA comprises:
    a. a 5' cap comprising $m_2^{7,3'-O}Gppp(m_1^{2'-O})ApG$ or 3'-O-Me-$m^7G(5')ppp(5')G$;
    b. a 5' UTR comprising (i) a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 4 and 6;
    c. a 3' UTR comprising (i) the nucleotide sequence of SEQ ID NO: 8, or (ii) a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO:8; and
    d. a poly-A tail comprising at least 100 nucleotides.
85. The RNA or use of claim 84, wherein the poly-A tail comprises SEQ ID NO: 66.
86. The RNA or use of any one of claims 56-85, wherein the method further comprises administering a further therapy.
87. The RNA or use of claim 86, wherein the further therapy comprises one or more selected from the group consisting of: (i) surgery to excise, resect, or debulk a tumor, (ii) immunotherapy, (iii) radiotherapy, and (iv) chemotherapy.
88. The RNA or use of claim 86 or 87, wherein the further therapy comprises administering a further therapeutic agent.

89. The RNA or use of claim 88, wherein the further therapeutic agent is an anti-cancer therapeutic agent.
90. The RNA or use of claim 86 or 87, wherein the further therapeutic agent is a checkpoint modulator.
91. The RNA or use of claim 90, 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.
92. The RNA or use of any one of claims 56-91, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.
93. The RNA or use of any one of claims 56-91, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.
94. The RNA or use of any one of claims 56-93, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.
95. The RNA or use of any one of claims 56-94, wherein the RNA is administered intra-tumorally or peri-tumorally.
96. The RNA or use of any one of claims 56-95, wherein the RNA is formulated for injection.
97. The RNA or use of any one of claims 86-96, wherein the further therapeutic agent is administered systemically.
98. The RNA or use of any one of claims 56-97, wherein the subject is a human.
99. The RNA or use of any one of claims 56-98, wherein the RNAs are administered at the same time.
100. The RNA or use of any one of claims 56-99, wherein the RNAs are administered via injection, wherein the RNAs are mixed together in liquid solution prior to injection.
101. The RNA or use of any one of claims 56-100, wherein the RNAs are administered by administering a composition comprising a combination of the RNAs.

102. The RNA or use of any one of claims 56-100, wherein treating or preventing a solid tumor comprises reducing the size of a tumor, preventing the reoccurrence of cancer in remission, or preventing cancer metastasis in a subject.

103. A composition or medical preparation comprising RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding an FLT3-L protein.

104. The composition according to claim 103.

105. The medical preparation according to claim 103.

106. The medical preparation or composition according to claims 103-105, wherein the RNA is in a ratio of 1:1:1 or 1:1:1:1, and wherein the ratio is validated by quantitative RT-PCR.

107. The medical preparation or composition according to claims 103-106, wherein the RNA integrity is greater than or equal to 70%.

108. The medical preparation or composition according to claims 103-107, wherein the medical preparation or composition comprises less than 250 ng DNA per the total mg of nucleic acid present.

109. The medical preparation or composition according to claims 103-108, wherein the IFNα protein is an IFNα2b protein.

110. The medical preparation or composition according to claims 103-109, wherein

(i) the RNA encoding an IL-12sc protein comprises the nucleotide sequence of SEQ ID NO: 17 or 18, 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: 17 or 18; and/or

(ii) the IL-12sc protein comprises the amino acid sequence of SEQ ID NO: 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:14; and/or

(iii) the RNA encoding an IL-12sc protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p40 portion of IL-12sc (nucleotides 1-984 of SEQ ID NO: 17 or 18) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the p30 portion of IL-12sc (nucleotides 1027-1623 of SEQ ID NO: 17 or 18) and further comprises nucleotides between the p40 and p35 portions encoding a linker polypeptide.

111. The medical preparation or composition according to claims 103-110, wherein

(i) the RNA encoding an IL-15 sushi protein comprises the nucleotide sequence of SEQ ID NO: 26, 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: 26; and/or

(ii) the IL-15 sushi protein 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; and/or

(iii) the RNA encoding an IL-15 sushi protein comprises a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the sushi domain of IL-15 receptor alpha (nucleotides 1-321 of SEQ ID NO: 26) and at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to mature IL-15 (nucleotides 382-729 of SEQ ID NO: 26) and optionally further comprises nucleotides between the sushi domain of IL-15 and the mature IL-15 encoding a linker polypeptide.

112. The medical preparation or composition of according to claims 103-111, wherein

(i) the RNA encoding an IFNα protein comprises the nucleotide sequence of SEQ ID NO: 22 or 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: 22 or 23 and/or

(ii) the IFNα protein comprises the amino acid sequence of SEQ ID NO: 19, 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: 19.

113. The medical preparation or composition according to claims 103-112, wherein

(i) the RNA encoding an FLT3-L protein comprises the nucleotide sequence of SEQ ID NO: 32, 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: 32; and/or

(ii) the FLT3-L protein comprises the amino acid sequence of SEQ ID NO: 30, 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: 30.

114. The medical preparation or composition according to claims 103-113, which is a pharmaceutical composition comprising the RNAs.

115. The medical preparation or composition of claim 114, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable carriers, diluents and/or excipients.

116. The medical preparation or composition according to claims 103-115, wherein the RNA is formulated as a liquid, formulated as a solid, or a combination thereof.

117. The medical preparation or composition according to claims 103-116, for pharmaceutical use.

118. The medical preparation or composition according to claims 103-117, wherein the pharmaceutical use comprises a therapeutic or prophylactic treatment of a disease or disorder.

119. The medical preparation or composition according to claims 103-118, wherein the therapeutic or prophylactic treatment of a disease or disorder comprises treating or preventing a solid tumor.

120. The medical preparation or composition of claim 119, wherein the solid tumor is a sarcoma, carcinoma, or lymphoma.

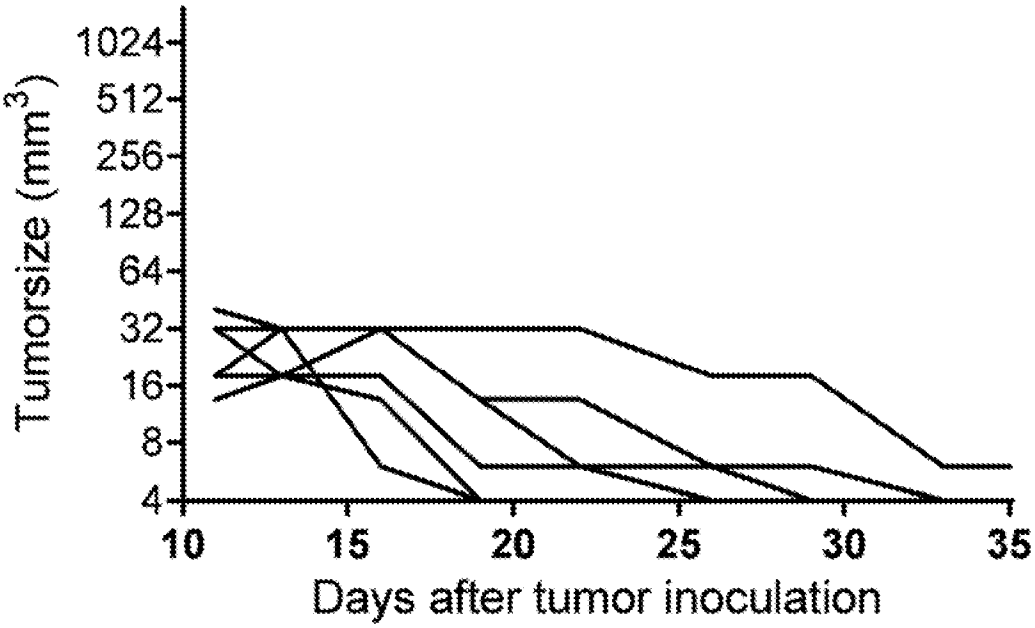
121. The medical preparation or composition of according to claims 119-120, wherein the solid tumor is in the lung, colon, ovary, cervix, uterus, peritoneum, testicles, penis, tongue, lymph node, pancreas, bone, breast, prostate, soft tissue, connective tissue, kidney, liver, brain, thyroid, or skin.

122. The medical preparation or composition of according to claims 103-121, wherein the solid tumor is an epithelial tumor, Hodgkin lymphoma (HL), non-Hodgkin lymphoma, prostate tumor, ovarian tumor, renal cell tumor, gastrointestinal tract tumor, hepatic tumor, colorectal tumor, tumor with vasculature, mesothelioma tumor, pancreatic tumor, breast tumor, sarcoma tumor, lung tumor, colon tumor, brain tumor, melanoma tumor, small cell lung tumor, neuroblastoma tumor, testicular tumor, carcinoma tumor, adenocarcinoma tumor, glioma tumor, seminoma tumor, retinoblastoma, or osteosarcoma tumor.

123. RNA for use in a method for treating or preventing a solid tumor in a subject, wherein the method comprises administering RNA encoding an IL-12sc protein, RNA

encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding a FLT3-L protein.

124. Use of RNA encoding an IL-12sc protein, RNA encoding an IL-15 sushi protein, RNA encoding an IFNα protein, and RNA encoding an FLT3-L for the treatment of solid tumor.


Tumorsize (mm3)
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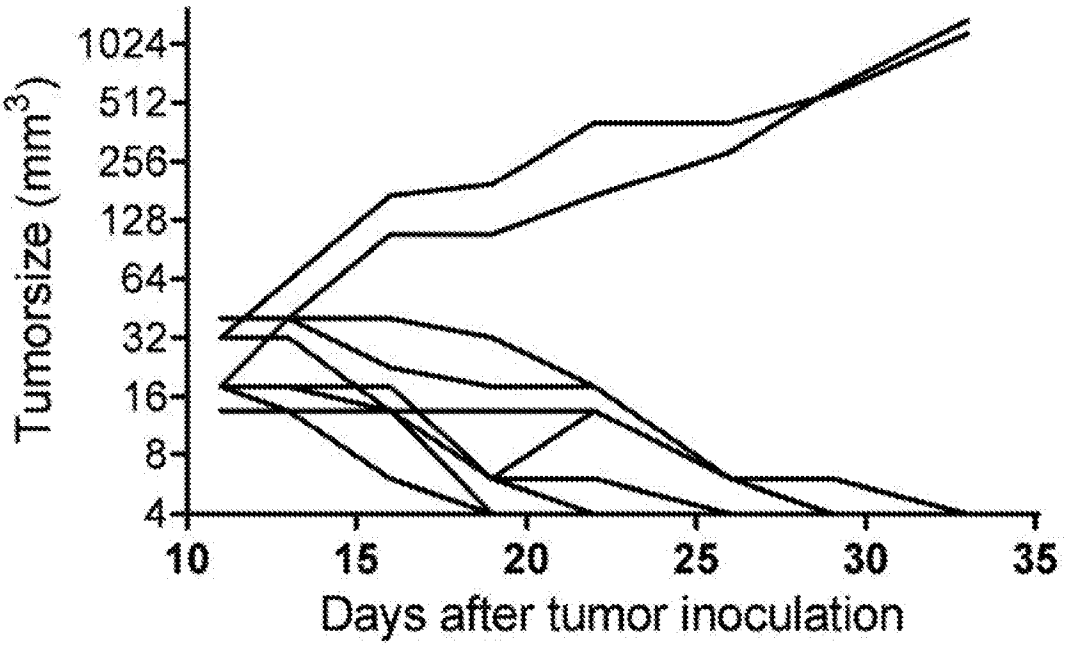
512
256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1A


Tumorsize (mm3)
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256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1B

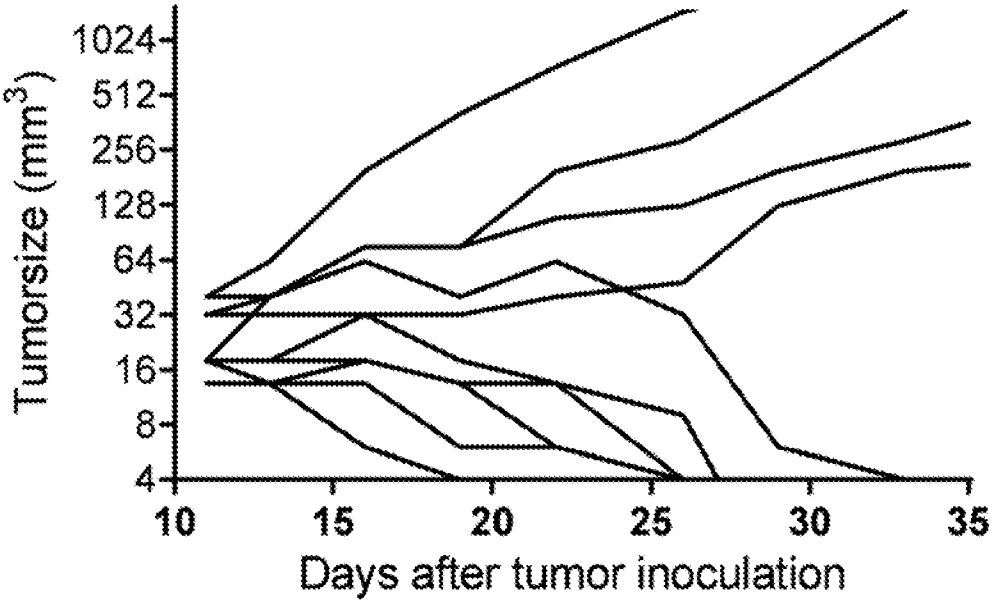
Tumorsize (mm3)
1024
512
256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1C

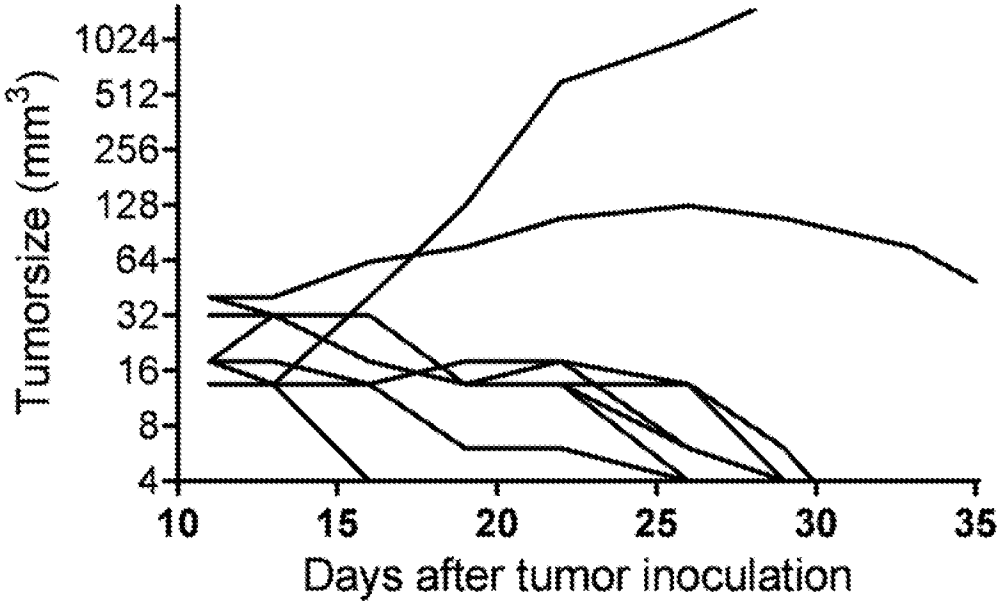
Tumorsize (mm3)
1024
512
256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1D

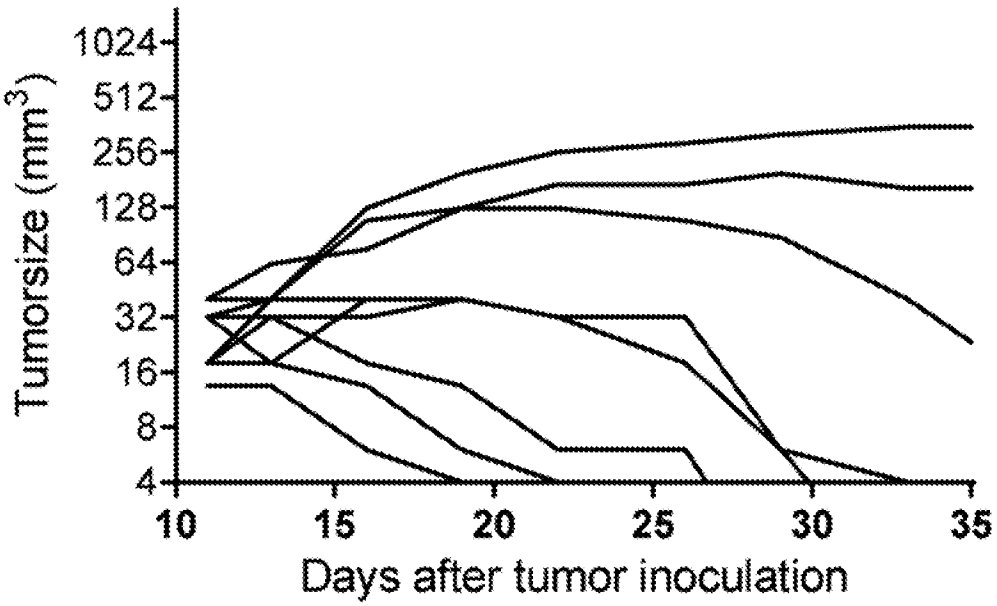
Tumorsize (mm3)
1024
512
256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1E

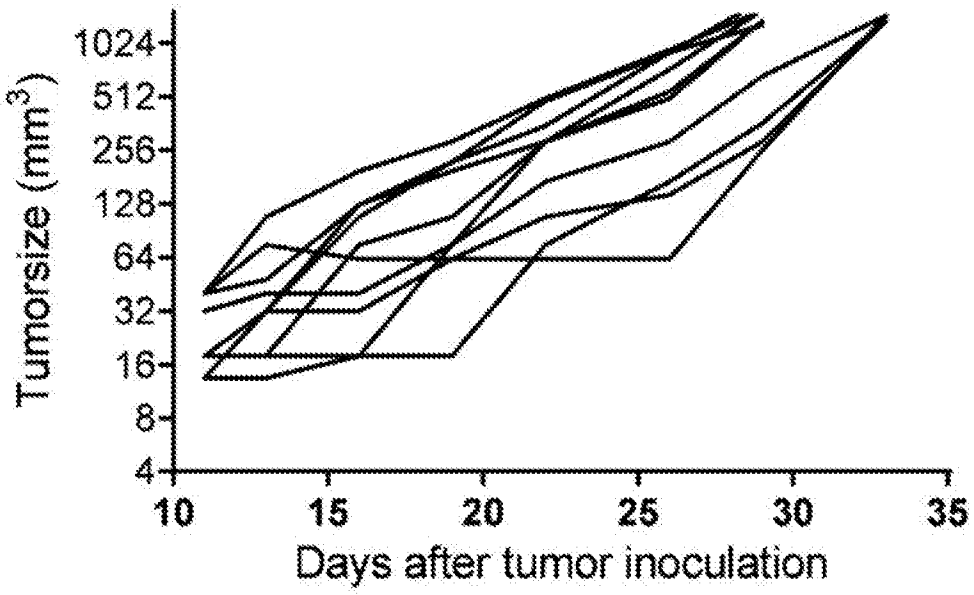
Tumorsize (mm3)
1024
512
256
128
64
32
16
8
4
10
15
20
25
30
35
Days after tumor inoculation

Fig. 1F

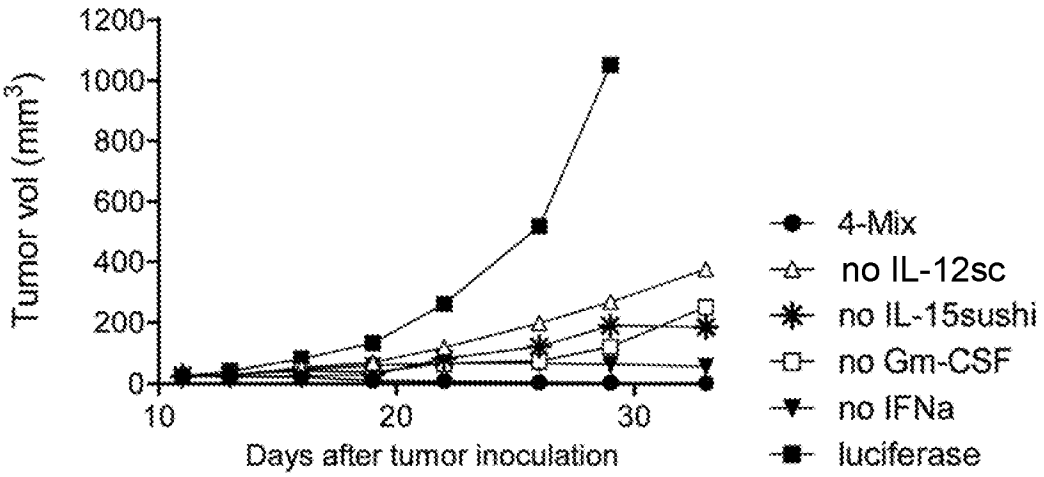
Tumor vol (mm3)
1200
1000
800
600
400
200
0
10
20
30
Days after tumor inoculation
4-Mix
no IL-12sc
no IL-15sushi
no Gm-CSF
no IFNa
luciferase

Fig. 1G

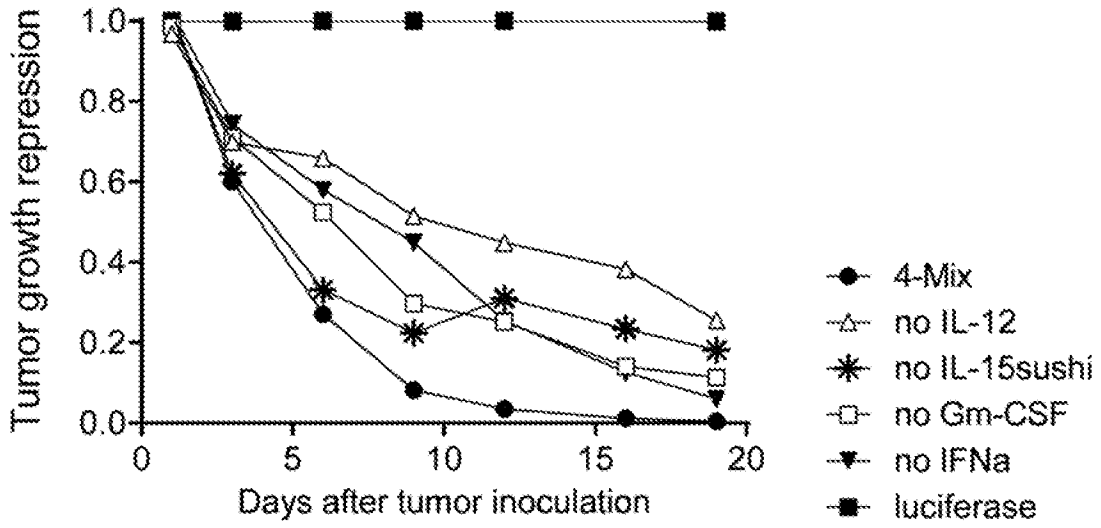
Tumor growth repression
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Days after tumor inoculation
4-Mix
no IL-12
no IL-15sushi
no Gm-CSF
no IFNa
luciferase

Fig. 1H

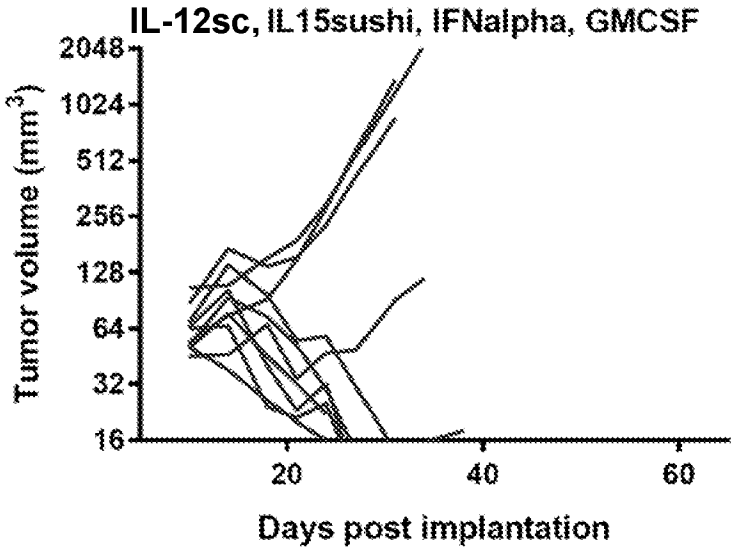
IL-12sc, IL15sushi, IFNalpha, GMCSF
Tumor volume (mm3)
2048
1024
512
256
128
64
32
16
20
40
60
Days post implantation

Fig. 2A

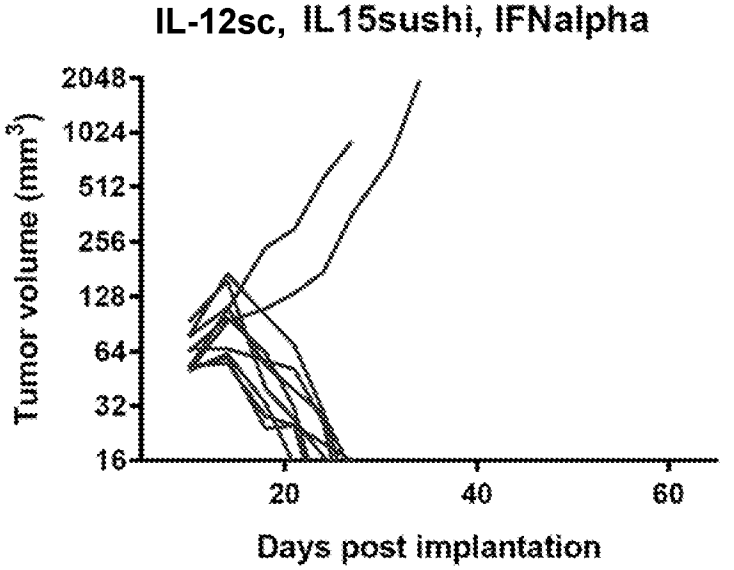
IL-12sc, IL15sushi, IFNalpha
Tumor volume (mm3)
2048
1024
512
256
128
64
32
16
20
40
60
Days post implantation

Fig. 2B

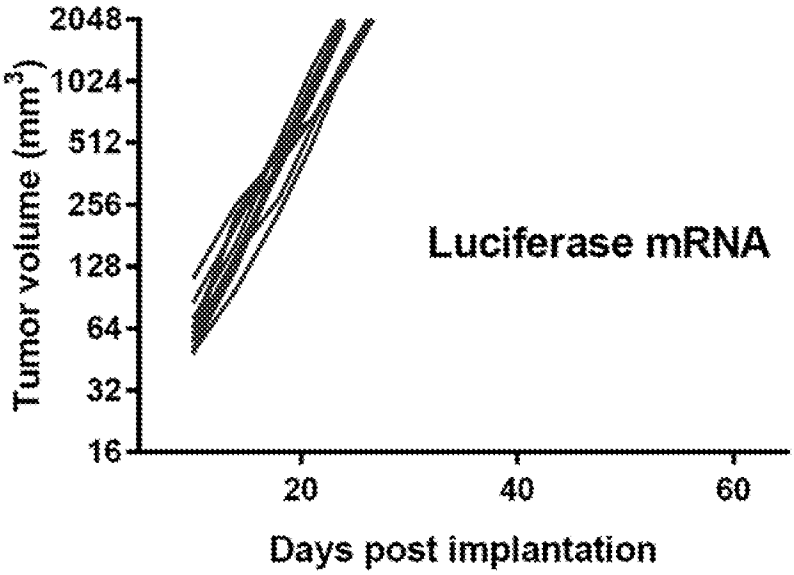
2048
1024
512
256
128
64
32
16
Tumor volume (mm3)
20
40
60
Days post implantation
Luciferase mRNA

Fig. 2C

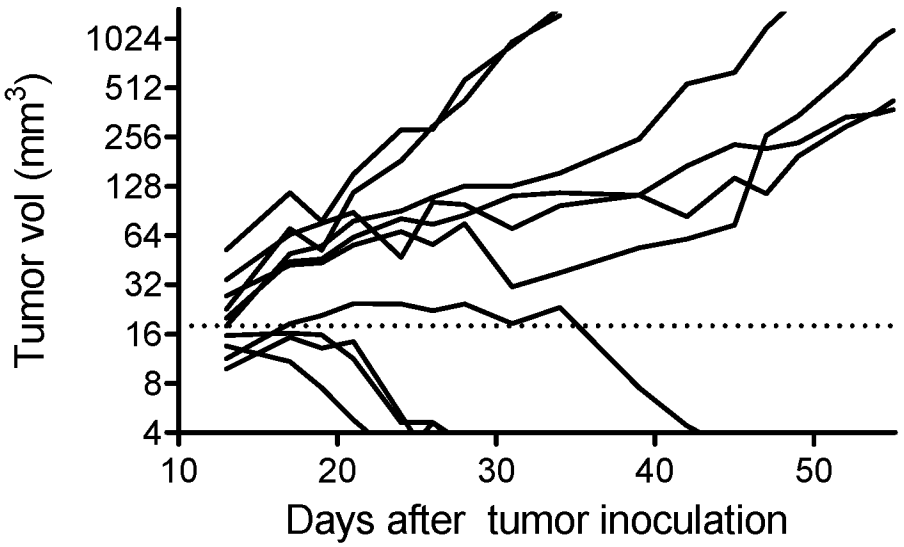
1024
512
256
128
64
32
16
8
4
Tumor vol (mm3)
10
20
30
40
50
Days after tumor inoculation

Fig. 3A

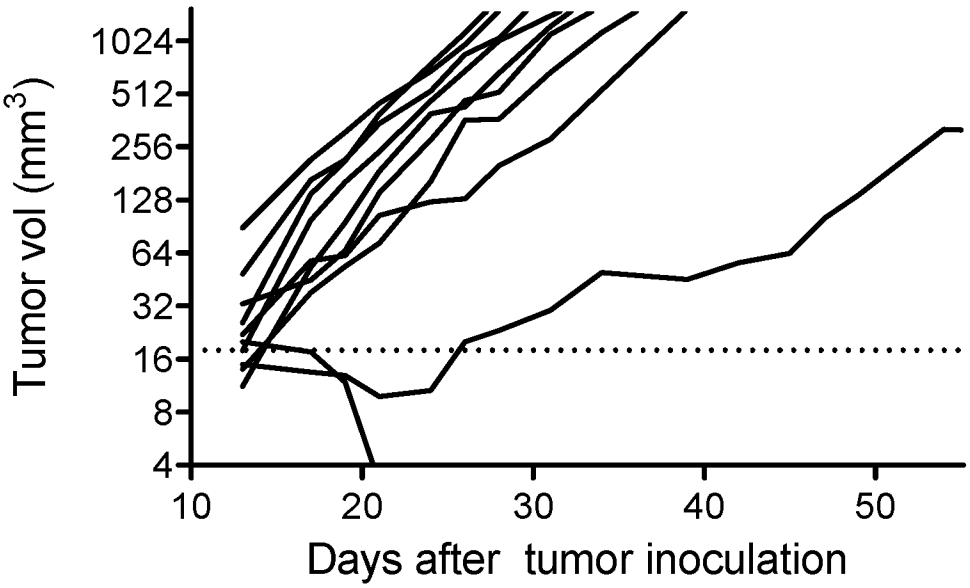
1024
512
256
128
64
32
16
8
4
Tumor vol (mm3)
10
20
30
40
50
Days after tumor inoculation

Fig. 3B

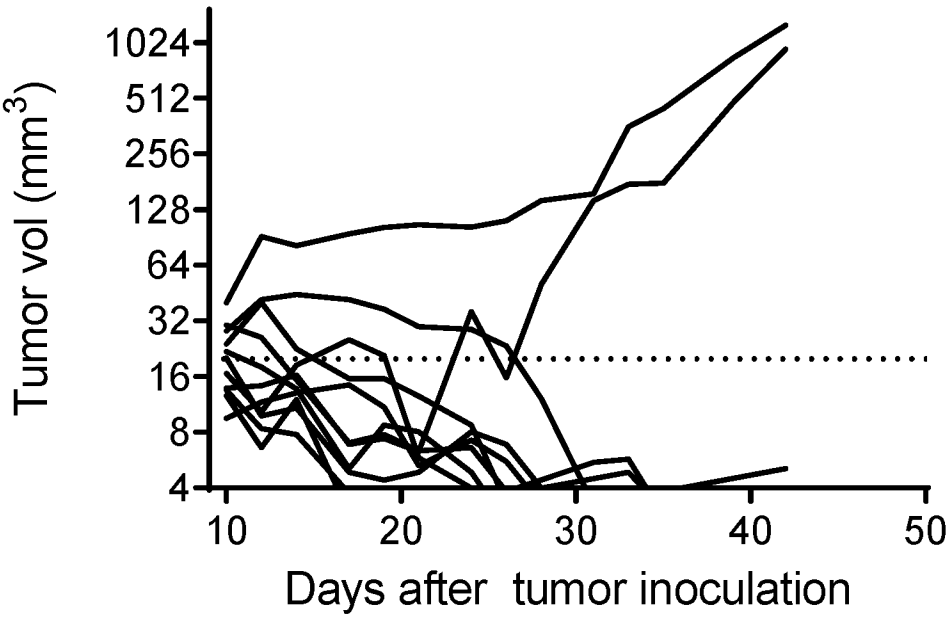
1024
512
256
128
64
32
16
8
4
Tumor vol (mm3)
10
20
30
40
50
Days after tumor inoculation

Fig. 3C

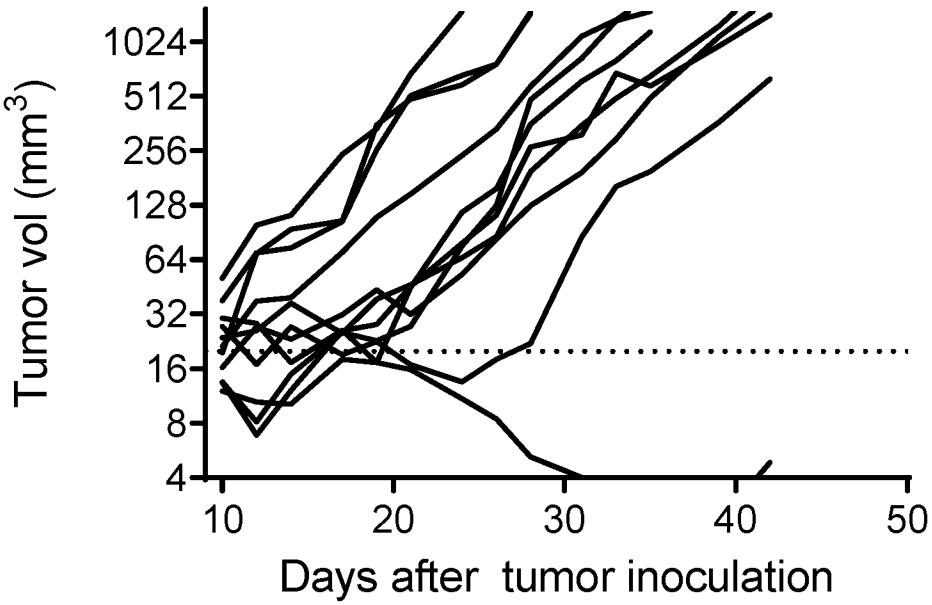
1024
512
256
128
64
32
16
8
4
Tumor vol (mm3)
10
20
30
40
50
Days after tumor inoculation

Fig. 3D

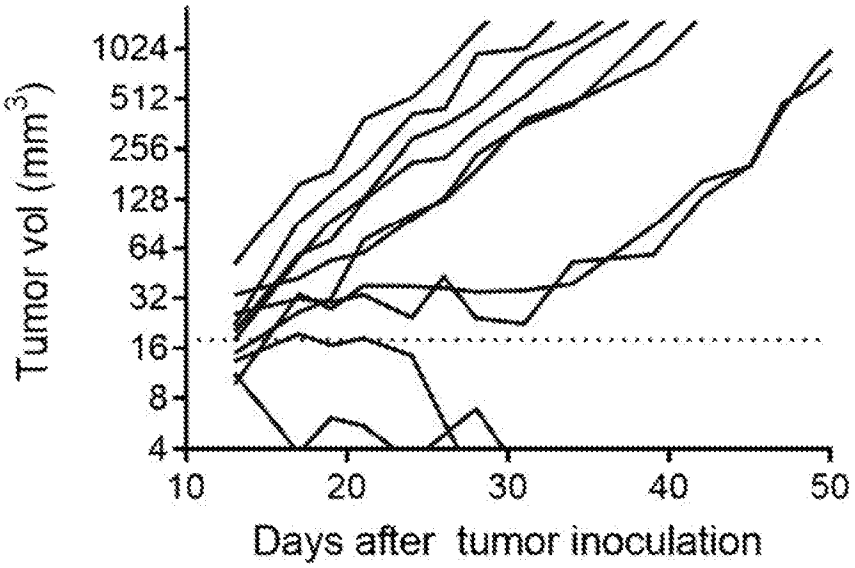
Tumor vol (mm3)
1024
512
256
128
64
32
16
8
4
10
20
30
40
50
Days after tumor inoculation

Fig. 3E

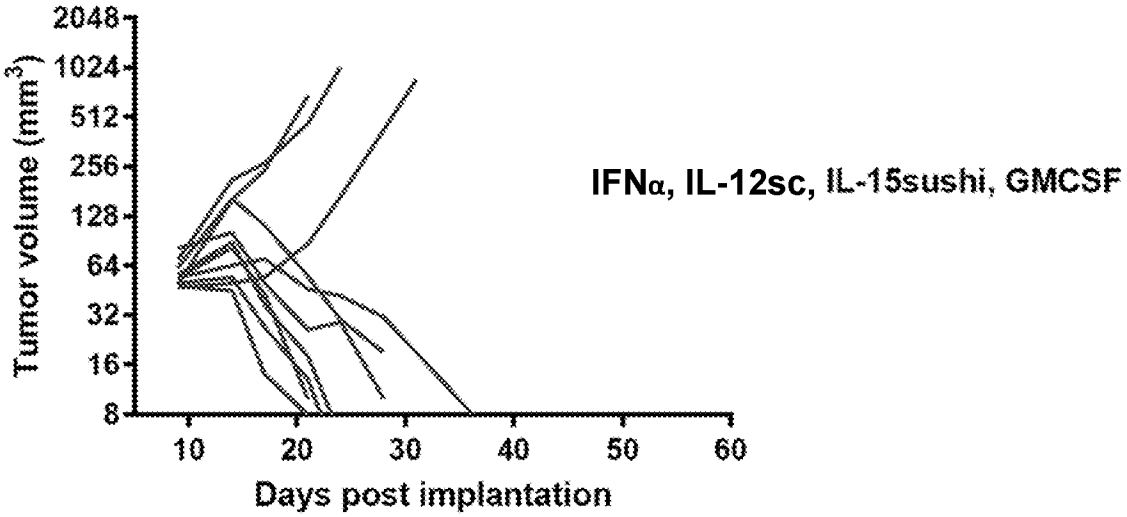
2048
1024
512
256
128
64
32
16
8
Tumor volume (mm3)
10
20
30
40
50
60
Days post implantation
IFNα, IL-12sc, IL-15sushi, GMCSF

Fig. 4A

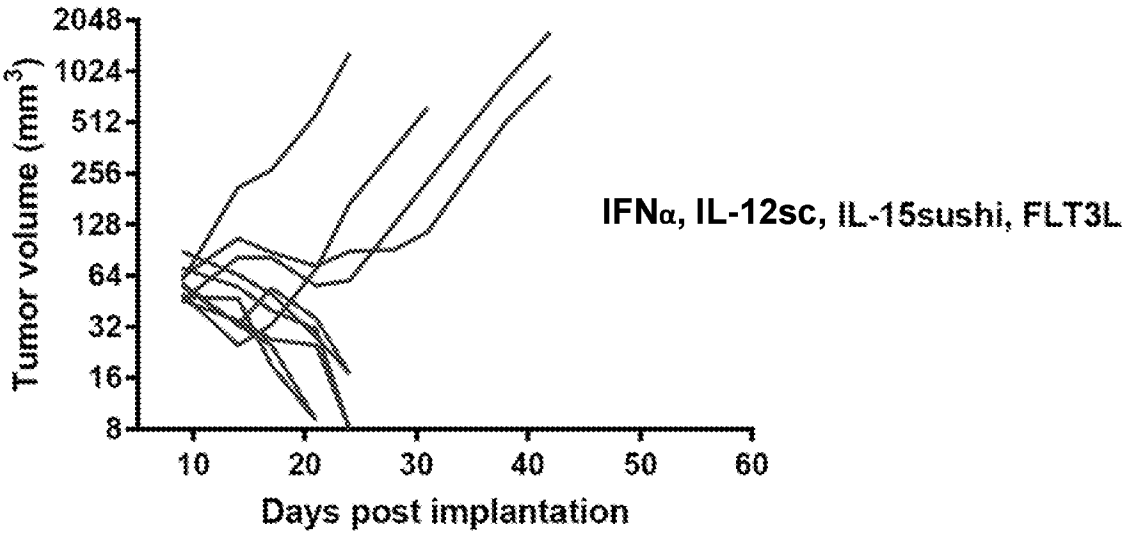
2048
1024
512
256
128
64
32
16
8
Tumor volume (mm3)
10
20
30
40
50
60
Days post implantation
IFNα, IL-12sc, IL-15sushi, FLT3L

Fig. 4B

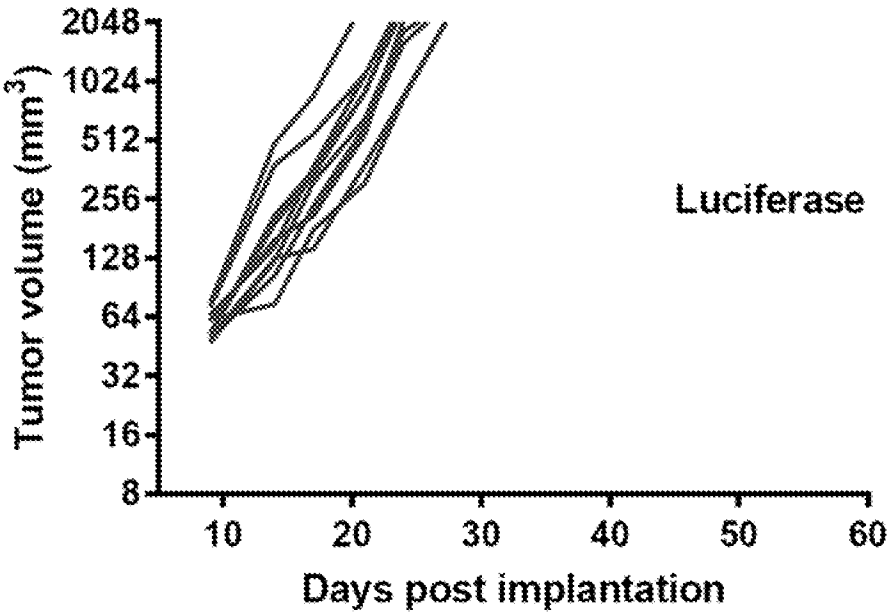
2048
1024
512
256
128
64
32
16
8
Tumor volume (mm3)
10
20
30
40
50
60
Days post implantation
Luciferase

Fig. 4C

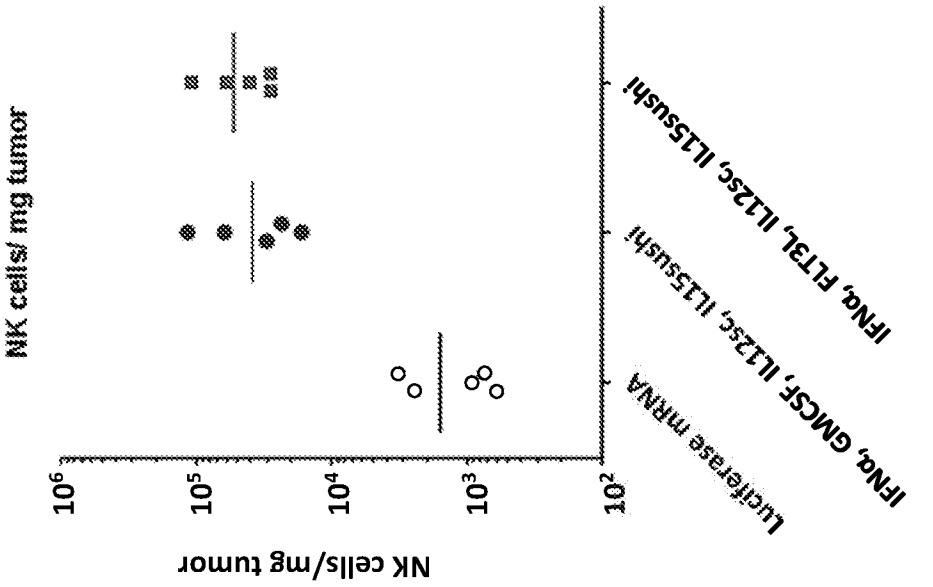
NK cells/ mg tumor
NK cells/mg tumor
Luciferase mRNA
IFNα, GMCSF, IL12sc, IL15sushi
IFNα, FLT3L, IL12sc, IL15sushi

Fig. 5B

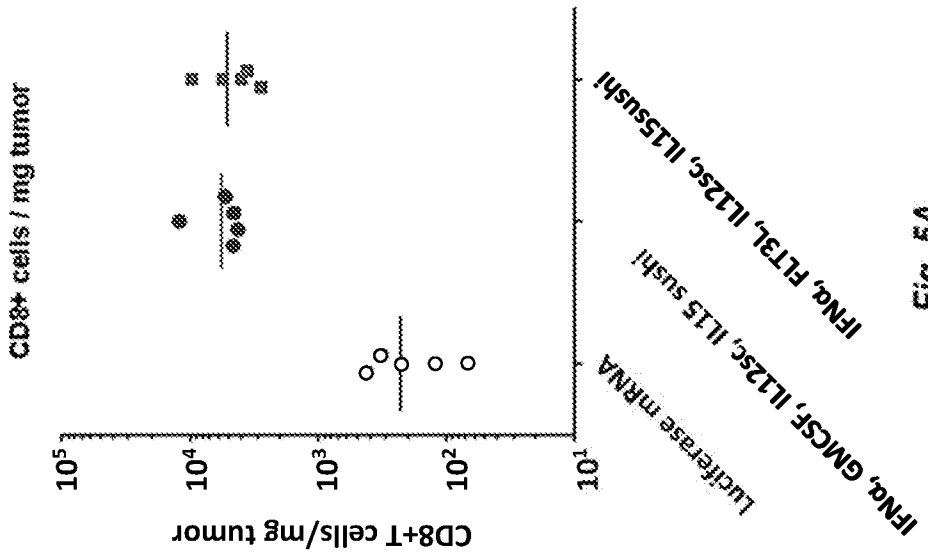
CD8+ cells / mg tumor
CD8+T cells/mg tumor
Luciferase mRNA
IFNα, GMCSF, IL12sc, IL15 sushi
IFNα, FLT3L, IL12sc, IL15sushi

Fig. 5A

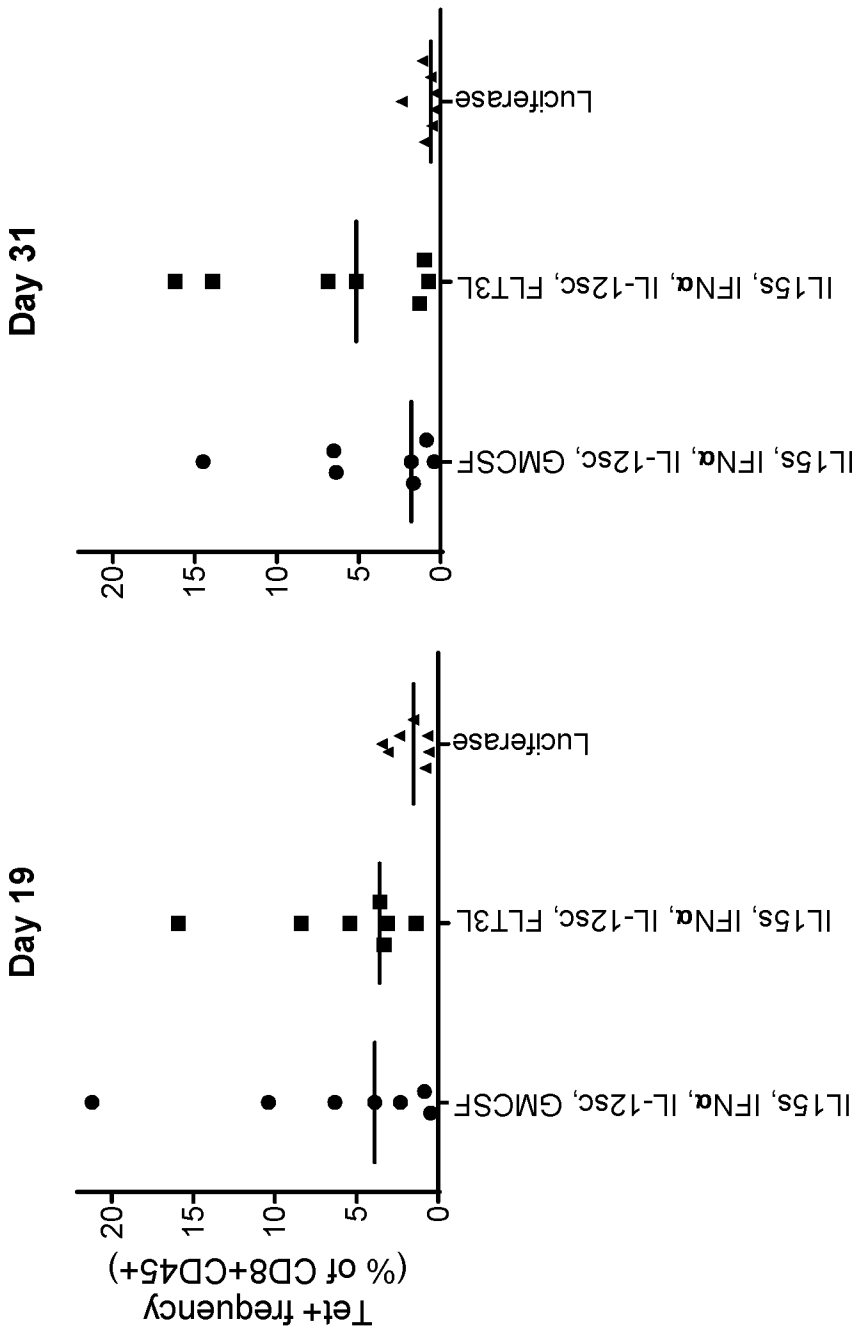
Day 19
Day 31
Tet+ frequency
(% of CD8+CD45+)
0
5
10
15
20
IL15s, IFNα, IL-12sc, GMCSF
IL15s, IFNα, IL-12sc, FLT3L
Luciferase

Fig. 6A

Fig. 6B

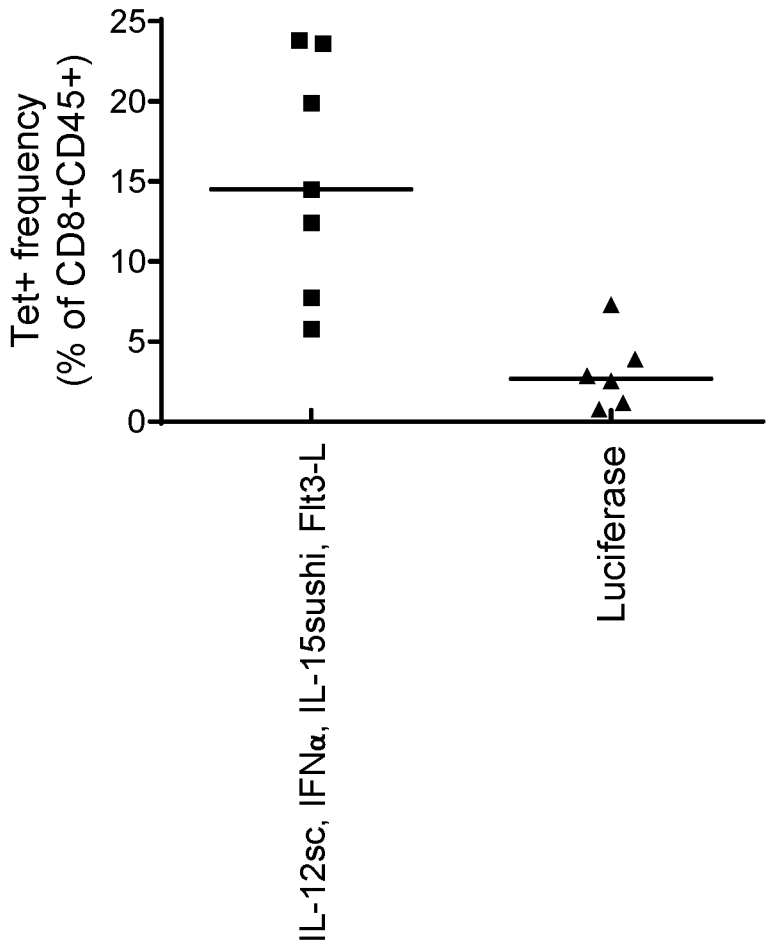
Tet+ frequency
(% of CD8+CD45+)
25
20
15
10
5
0
IL-12sc, IFNα, IL-15sushi, Flt3-L
Luciferase

Fig. 6C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/047819

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/54 C07K14/56 A61K38/19 A61K38/20 A61K31/70 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2017/080104 A1 (IRVINE DARRELL J [US] ET AL) 23 March 2017 (2017-03-23)	1,3-11, 13-57, 59-64, 66-102
A	abstract paragraphs [0034], [0036]	2,12,58, 65, 103-124

Y	US 2016/311879 A1 (SOPCZYNSKI JOAN MAZZARELLI [US] ET AL) 27 October 2016 (2016-10-27)	1,3-11, 13-57, 59-64, 66-102
A	abstract paragraphs [0008], [0016], [0020]	2,12,58, 65, 103-124

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2019	31/10/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Weisser, Dagmar

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/047819

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	THEOFANIS FLOROS ET AL: "Anticancer Cytokines: Biology and Clinical Effects of Interferon-[alpha]2, Interleukin (IL)-2, IL-15, IL-21, and IL-12", SEMINARS IN ONCOLOGY, vol. 42, no. 4, 1 August 2015 (2015-08-01) , pages 539-548, XP055464843, US ISSN: 0093-7754, DOI: 10.1053/j.seminoncol.2015.05.015	1,3-11, 13-57, 59-64, 66-102
A	the whole document	2,12,58, 65, 103-124

Y	HERNANDEZ-ALCOCEBA R ET AL: "Cytokines for the treatment of gastrointestinal cancers: Clinical experience and new perspectives", EXPERT OPINION ON INVESTIGATIONAL DRUGS, INFORMA HEALTHCARE, UK, vol. 22, no. 7, 1 January 2013 (2013-01-01), pages 827-841, XP009178899, ISSN: 1354-3784, DOI: 10.1517/13543784.2013.793307	1,3-11, 13-57, 59-64, 66-102
A	the whole document	2,12,58, 65, 103-124

T	WO 2018/160540 A1 (SANOFI SA [FR]; BIONTECH RNA PHARMACEUTICALS GMBH [DE]) 7 September 2018 (2018-09-07) the whole document	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/047819

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