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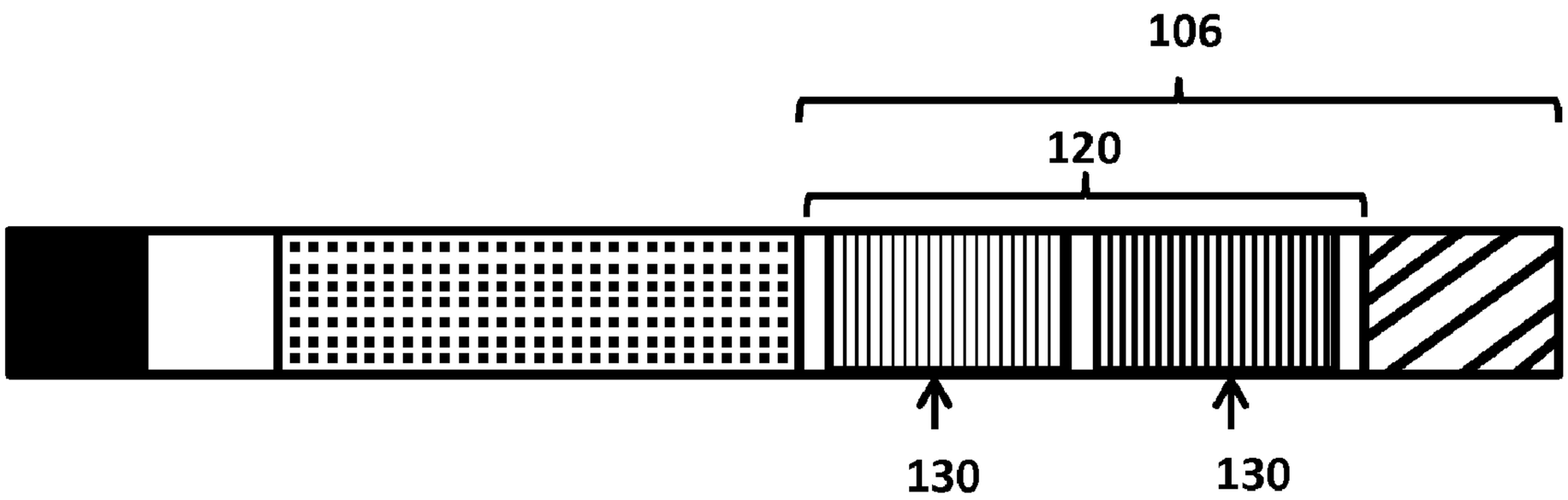
(54) Title: SIGNAL-SENSOR POLYNUCLEOTIDES FOR THE ALTERATION OF CELLULAR PHENOTYPES

**FIGURE 2**




(57) Abrégé/Abstract:
The invention relates to compositions and methods for the preparation, manufacture and therapeutic use of signal-sensor polynucleotides, primary transcripts and mmRNA molecules.

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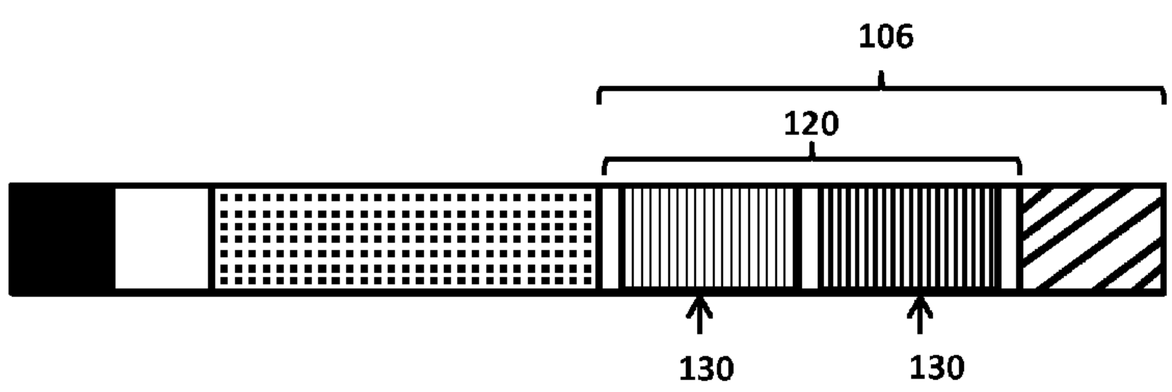
**FIGURE 2**




(57) Abstract: The invention relates to compositions and methods for the preparation, manufacture and therapeutic use of signal-sensor polynucleotides, primary transcripts and mmRNA molecules.

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# DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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# JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 312

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# SIGNAL-SENSOR POLYNUCLEOTIDES FOR THE ALTERATION OF CELLULAR PHENOTYPES

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Provisional Application No. 61,753,661, filed January 17, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; U.S. Provisional Application No. 61/754,159, filed January 18, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; U.S. Provisional Application No. 61/781,097, filed March 14, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; U.S. Provisional Application No. 61/829,334, filed May 31,2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; U.S. Provisional Application No. 61/839,893, filed June 27, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; U.S. Provisional Application No. 61/842,733, filed July 3, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; and U.S. Provisional Application No. 61/857,304, filed July 23, 2013, entitled Signal-Sensor Polynucleotides for the Alternation of Cellular Phenotypes and Microenvironments; the contents of each of which is herein incorporated by reference in its entirety.

## REFERENCE TO SEQUENCE LISTING

**[0002]** The present application is being filed along with a Sequence Listing in electronic format. The Sequence listing file, entitled M37PCT.txt, was created on September 30, 2013 and is 9,748,473 bytes in size. The information in electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

## FIELD OF THE INVENTION

**[0003]** The invention relates to compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of signal-sensor polynucleotides, primary constructs and mRNA molecules for the alteration of cellular phenotypes and microenvironments.

## BACKGROUND OF THE INVENTION

**[0004]** Cancer is a disease characterized by uncontrolled cell division and growth within the body. In the United States, roughly a third of all women and half of all men will experience cancer in their lifetime. Polypeptides are involved in every aspect of the disease including cancer cell biology (carcinogenesis, cell cycle suppression, DNA repair and angiogenesis), treatment (immunotherapy, hormone manipulation, enzymatic inhibition), diagnosis and determination of cancer type (molecular markers for breast, prostate, colon and cervical cancer for example). With the host of undesired consequences brought about by standard treatments such as chemotherapy and radiotherapy used today, genetic therapy for the manipulation of disease-related peptides and their functions provides a more targeted approach to disease diagnosis, treatment and management.

**[0005]** To this end, it has been previously shown that certain modified mRNA sequences have the potential as therapeutics with benefits beyond just evading, avoiding or diminishing the immune response. Such studies are detailed in published co-pending International Publication No WO2012019168 filed August 5, 201, International Publication No WO2012045082 filed October 3, 2011, International Publication No WO2012045075 filed October 3, 2011, International Publication No WO2013052523 filed October 3, 2012, and International Publication No WO2013090648 filed December 14, 2012 the contents of which are incorporated herein by reference in their entirety.

**[0006]** The use of modified polynucleotides in the fields of antibodies, viruses, veterinary applications and a variety of in vivo settings have been explored and are disclosed in, for example, co-pending and co-owned U.S. Provisional Patent Application No 61/618,862, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Biologics; U.S. Provisional Patent Application No 61/681,645, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Biologics; U.S. Provisional Patent Application No 61/737,130, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Biologics; U.S. Provisional Patent Application No 61/618,866, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Antibodies; U.S. Provisional Patent Application No 61/681,647, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Antibodies; U.S. Provisional

Patent Application No 61/737,134, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Antibodies; U.S. Provisional Patent Application No 61/618,868, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Vaccines; U.S. Provisional Patent Application No 61/681,648, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Vaccines; U.S. Provisional Patent Application No 61/737,135, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Vaccines; U.S. Provisional Patent Application No 61/618,870, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides; U.S. Provisional Patent Application No 61/681,649, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides; U.S. Provisional Patent Application No 61/737,139, filed December 14, 2012, Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides; U.S. Provisional Patent Application No 61/618,873, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins; U.S. Provisional Patent Application No 61/681,650, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins; U.S. Provisional Patent Application No 61/737,147, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins; U.S. Provisional Patent Application No 61/618,878, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins; U.S. Provisional Patent Application No 61/681,654, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins; U.S. Provisional Patent Application No 61/737,152, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins; U.S. Provisional Patent Application No 61/618,885, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins; U.S. Provisional Patent Application No 61/681,658, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins; U.S. Provisional Patent Application No 61/737,155, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins; U.S. Provisional Patent Application No 61/618,896, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins; U.S.

Provisional Patent Application No 61/668,157, filed July 5, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins; U.S. Provisional Patent Application No 61/681,661, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins; U.S. Provisional Patent Application No 61/737,160, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins; U.S. Provisional Patent Application No 61/618,911, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins; U.S. Provisional Patent Application No 61/681,667, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins; U.S. Provisional Patent Application No 61/737,168, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins; U.S. Provisional Patent Application No 61/618,922, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins; U.S. Provisional Patent Application No 61/681,675, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins; U.S. Provisional Patent Application No 61/737,174, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins; U.S. Provisional Patent Application No 61/618,935, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/681,687, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/737,184, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/618,945, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/681,696, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/737,191, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/618,953, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/681,704, filed August 10, 2012, entitled Modified

Polynucleotides for the Production of Proteins Associated with Human Disease; U.S. Provisional Patent Application No 61/737,203, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; US Provisional Patent Application No 61/681,720, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Cosmetic Proteins and Peptides; US Provisional Patent Application No 61/737,213 , filed December 14, 2012, entitled Modified Polynucleotides for the Production of Cosmetic Proteins and Peptides; US Provisional Patent Application No. 61/681,742, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Oncology-Related Proteins and Peptides; International Application No PCT/US2013/030062, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Biologics and Proteins Associated with Human Disease; US Patent Application No 13/791,922, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Biologics and Proteins Associated with Human Disease; International Application No PCT/US2013/030063, filed March 9, 2013, entitled Modified Polynucleotides; International Application No. PCT/US2013/030064, entitled Modified Polynucleotides for the Production of Secreted Proteins; US Patent Application No 13/791,921, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Secreted Proteins; International Application No PCT/US2013/030059, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Membrane Proteins; International Application No. PCT/US2013/030066, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins; International Application No. PCT/US2013/030067, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Nuclear Proteins; International Application No. PCT/US2013/030060, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Proteins; International Application No. PCT/US2013/030061, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; US Patent Application No 13/791,910, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; International Application No. PCT/US2013/030068, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Cosmetic Proteins and Peptides; and International Application No.

PCT/US2013/030070, filed March 9, 2013, entitled Modified Polynucleotides for the Production of Oncology-Related Proteins and Peptides; International Patent Application No. PCT/US2013/031821, filed March 15, 2013, entitled In Vivo Production of Proteins; the contents of each of which are herein incorporated by reference in their entireties.

**[0007]** Formulations and delivery of modified polynucleotides are described in, for example, co-pending and co-owned International Publication No WO2013090648, filed December 14, 2012, entitled Modified Nucleoside, Nucleotide, Nucleic Acid Compositions and US Publication No US20130156849, filed December 14, 2012, entitled Modified Nucleoside, Nucleotide, Nucleic Acid Compositions; the contents of each of which are herein incorporated by reference in their entireties.

**[0008]** The next generation of therapeutics must also address the complex cellular microenvironment of the cancer and have the capacity for cell, tissue, organ or patient stratification, whether structurally or functionally.

**[0009]** The present invention addresses this need by providing nucleic acid based compounds or polynucleotide-encoding nucleic acid-based compounds (e.g., signal-sensor polynucleotides) which encode a polypeptide of interest and which have structural and/or chemical features that allow for greater selectivity, profiling or stratification along defineable disease characteristics or metrics.

## SUMMARY OF THE INVENTION

**[0010]** Described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of signal-sensor polynucleotide molecules encoding at least one oncology-related polypeptide of interest. Such signal-sensor polynucleotides may be chemically modified mRNA (mmRNA) molecules.

**[0011]** The present invention provides an isolated signal-sensor polynucleotide comprising a region encoding an oncology-related polypeptide of interest that functions, when translated, to send a death or survival signal. Such death or survival signals include those which (i) alter (increase or decrease) the expression of one or more proteins, nucleic acids, or non-coding nucleic acids, (ii) alter the binding properties of biomolecules within the cell, and/or (iii) perturb the cellular microenvironment in a therapeutically benificial way.

**[0012]** Optionally, the signal-sensor polnucleotide may also encode in a flanking region, one or more sensor sequences. Such sensor sequences function to "sense" the cell, tissue or ogan microenvironment and confer upon the signal-sensor polynucleotide an altered expression or half life profile (increased or decreased) depending on the interactions of the sensor sequence with the cell, tissue or organ microenvironment.

**[0013]** In one aspect, provided herein are signal -sensor polynucleotide comprising, a first region of linked nucleosides, a first flanking region located 5' relative to said first region and a second flanking region located 3' relative to said first region. The first region may encode an oncology-related polypeptide of interest such as, but not limited to, SEQ ID NOs: 1321-2487, 6611-6616 and 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516 and 7517 and the first flanking region may include a sequence of linked nucleosides such as, but not limited to, the native 5' untranslated region (UTR) of any of the nucleic acids that encode any of SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516, 7517, SEQ ID NO: 1-4 and functional variants thereof. The first region may comprise at least an open reading frame of a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 2488-2496, 6617-6621, 7348-7354, 7362-7489, 7491, 7494, 7506, 7511 and 7513.

**[0014]** The second flanking region may include a sequence of linked nucleosides such as, but not limited to, the native 3' UTR of any of the nucleic acids that encode any of SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516, 7517, SEQ ID NO: 5-21 and functional variants thereof, and one or more sensor sequences located such as, but not limited to, SEQ ID NOs: 3529-4549, SEQ ID NOs: 5571-6591 and functional variants thereof. The signal-sensor polynucleotide may also include a 3' tailing sequence of linked nucleosides.

**[0015]** In another aspect, provided herein is a signal-sensor polynucleotide which comprises an mRNA encoding an oncology-related polypeptide of interest and one or more sensor sequences such as, but not limited to, SEQ ID NOs: 3529-4549, SEQ ID NOs: 5571-6591 and functional variants thereof. The oncology-related polypeptide of interest may be, but is not limited to, SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516 and 7517. The mRNA may include at least one open reading frame of a nucleic acid sequence selected from the group consisting of

SEQ ID NOs: 2488-2496, 6617-6621, 7348-7354, 7362-7489, 7491, 7494, 7506, 7511 and 7513.

**[0016]** The signal-sensor polynucleotides may comprise one, two, three or more than three stop codons. In one aspect, the signal-sensor polynucleotides comprise two stop codons. As a non-limiting example, the first stop codon is "TGA" and the second stop codon is selected from the group consisting of "TAA," "TGA" and "TAG." In another aspect, signal-sensor polynucleotides comprise three stop codons.

**[0017]** The signal-sensor polynucleotides may have a 3' tailing sequence of linked nucleosides such as, but not limited to, a poly-A tail of at least 140 nucleotides, a triple helix, and a poly A-G quartet.

**[0018]** The signal-sensor polynucleotides may have a 5'cap such as, but not limited to, Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

**[0019]** In one aspect, the signal-sensor polynucleotides may include at least one chemical modification such as, but not limited to, modifications located on one or more of a nucleoside and/or the backbone of the nucleotides. In one embodiment, the signal-sensor polynucleotides comprise a pseudouridine analog such as, but not limited to, 1-carboxymethyl-pseudouridine, 1-propynyl-pseudouridine, 1-taurinomethyl-pseudouridine, 1-taurinomethyl-4-thio-pseudouridine, 1-methyl-pseudouridine ($m^1\psi$), 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, dihydropseudouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\ \psi$), and 2'-O-methyl-pseudouridine ($\psi m$). In another embodiment, the signal-sensor polynucleotides comprise the pseudouridine analog 1-methylpseudouridine. In yet another embodiment, the signal-sensor polynucleotides comprise the pseudouridine analog 1-methylpseudouridine and the modified nucleoside 5-methylcytidine.

**[0020]** In another aspect, the signal sensor-polynucleotides may include at least two chemical modifications such as, but not limited to, modifications located on one or more of a nucleoside and/or the backbone of the nucleotides. As a non-limiting example, the signal-sensor polynucleotide comprises the chemical modifications 1-methylpseudouridine and 5-methylcytidine.

**[0021]** The signal-sensor polynucleotides may comprise at least one translation enhancer element (TEE) such as, but not limited to, TEE-001 – TEE-705.

**[0022]** In one aspect, the signal-sensor polynucleotide encodes a factor modulating the affinity between HIF subunits and/or HIF-dependent gene expression such as, but not limited to, SEQ ID NO: 6611-6616.

**[0023]** The signal-sensor polynucleotides may be purified and/or formulated.

**[0024]** Employing the signal-sensor polynucleotides, the present invention provides a method of treating a disease, disorder and/or condition in a subject in need thereof by increasing the level of an oncology-related polypeptide of interest comprising administering to said subject an isolated signal-sensor polynucleotide encoding said oncology-related polypeptide. The disease, disorder and/or condition may include, but is not limited to, adrenal cortical cancer, advanced cancer, anal cancer, aplastic anemia, bileduct cancer, bladder cancer, bone cancer, bone metastasis, brain tumors, brain cancer, breast cancer, childhood cancer, cancer of unknown primary origin, Castleman disease, cervical cancer, colon/rectal cancer, endometrial cancer, esophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, renal cell carcinoma, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, lung carcinoid tumor, lymphoma of the skin, malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma in adult soft tissue, basal and

squamous cell skin cancer, melanoma, small intestine cancer, stomach cancer, testicular cancer, throat cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor and secondary cancers caused by cancer treatment.

**[0025]** The present invention provides a method of reducing, eliminating,or preventing tumor growth in a subject in need thereof by increasing the level of an oncology-related polypeptide of interest comprising administering to said subject an isolated signal-sensor polynucleotide encoding said oncology-related polypeptide. The tumor growth may be associated with or results from a disease, disorder and/or condition such as, but not limited to, adrenal cortical cancer, advanced cancer, anal cancer, aplastic anemia, bileduct cancer, bladder cancer, bone cancer, bone metastasis, brain tumors, brain cancer, breast cancer, childhood cancer, cancer of unknown primary origin, Castleman disease, cervical cancer, colon/rectal cancer, endometrial cancer, esophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, renal cell carcinoma, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, lung carcinoid tumor, lymphoma of the skin, malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma in adult soft tissue, basal and squamous cell skin cancer, melanoma, small intestine cancer, stomach cancer, testicular cancer, throat cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor and secondary cancers caused by cancer treatment.

**[0026]** The present invention provides a method of reducing and/or ameriorating at least one symptom of cancer in a subject in need thereof by increasing the level of a polypeptide of interest comprising administering to said subject an isolated signal-sensor

polynucleotide encoding said oncology-related polypeptide. Non-limiting examples of symptoms include weakness, aches and pains, fever, fatigue, weight loss, blood clots, increased blood calcium levels, low white blood cell count, short of breath, dizziness, headaches, hyperpigmentation, jaundice, erthema, pruritis, excessive hair growth, change in bowel habits, change in bladder function, long-lasting sores, white patches inside the mouth, white spots on the tongue, unusual bleeding or discharge, thickening or lump on parts of the body, indigestion, trouble swallowing, changes in warts or moles, change in new skin and nagging cough and hoarseness.

**[0027]** The present invention provides a method of preferentially inducing cell death in cancer cells in a tissue or organ comprising contacting the tissue or organ with a signal-sensor polynucleotide encoding an oncology-related polypeptide whose expression triggers apoptosis or cell death and at least one microRNA binding site of a microRNA where the expression of the microRNA in the cancer cell is lower than the expression of the mircroRNA in normal non-cancerous cells.

**[0028]** The signal-sensor polynucleotide may be administered at a total daily dose of between 0.001 ug and 150 ug. Administration of a signal-sensor polynucleotide may be by injection, topical administration, ophthalmic administration or intranasal administration. In one aspect, administration may be by injection such as, but not limited to, intradermal, subcutaneous and intramuscular. In another aspect, administration may be topical such as, but not limited to, using creams, lotions, ointments, gels, sprays, solutions and the like.

**[0029]** The details of various embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0030]** The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

**[0031]** FIG. 1 is a schematic of a primary construct of the present invention.

**[0032]** FIG. 2 is an expanded schematic of the second flanking region of a primary construct of the present invention illustrating the signal-sensor elements of the polynucleotide.

**[0033]** FIG. 3 is a gel profile of Apoptosis-Inducing Factor short (AIFsh) protein from AIFsh modified mRNA in mammals. Figure 3A shows the expected size of AIFsh. Figure 3B shows the expected size of AIFsh.

**[0034]** FIG. 4 is a gel profile of Siah E3 ubiquitin protein ligase 1 (SIAH1) protein from SIAH1 modified mRNA in mammals. Figure 4A shows the expected size of SIAH1. Figure 4B shows the expected size of SIAH1.

**[0035]** FIG. 5 is a gel profile of constitutively active (C.A.) caspase 3 (also known as reverse caspase 3 (Rev-Caspase 3)) protein from C.A. caspase 3 modified mRNA in mammals. Figure 5A shows the expected size of C.A. caspase 3. Figure 5B shows the expected size of C.A. caspase 3.

**[0036]** FIG. 6 is a gel profile of Granulysin protein from granulysin modified mRNA in mammals. Figure 6A shows the expected size of granulysin. Figure 6B shows the expected size of granulysin.

**[0037]** FIG. 7 is a western blot of C.A. caspase 3 and C.A. caspase 6. Figure 7A shows protein from C.A. caspase 3 modified mRNA fully modified with 5-methylcytidine and 1-methylpseudouridine or fully modified with 1-methylpseudouridine. Figure 7B shows protein from C.A. caspase 6 modified mRNA fully modified with 5-methylcytidine and 1-methylpseudouridine or fully modified with 1-methylpseudouridine.

## DETAILED DESCRIPTION

**[0038]** It is of great interest in the fields of therapeutics, diagnostics, reagents and for biological assays to be able to deliver a nucleic acid, e.g., a ribonucleic acid (RNA) inside a cell, whether *in vitro*, *in vivo, in situ* or *ex vivo*, such as to cause intracellular translation of the nucleic acid and production of an encoded polypeptide of interest. Of particular importance is the delivery and function of a non-integrative polynucleotide.

**[0039]** Described herein are compositions (including pharmaceutical compositions) and methods for the design, preparation, manufacture and/or formulation of polynucleotides encoding one or more polypeptides of interest. Also provided are systems, processes,

devices and kits for the selection, design and/or utilization of the polynucleotides encoding the polypeptides of interest described herein.

**[0040]** To this end, polypeptides of the present invention are encoded by a new class of polynucleotide therapeutics, termed "signal-sensor polynucleotides" which are particularly useful in the stratification, profiling and/or personalization of the polynucleotide therapeutice (e.g., mRNA) and which are tailored to a particular cell type, disease or cell microenvironment or biological profile.

**[0041]** It is known that cancers exhibit diverse gene expression patterns, physicochemical environments and metastatic or motility behaviors and according to Hanahan and Weinberg (Cell, 2011, 144:646-674) there are six hallmarks of cancer. These include sustaining a proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. These hallmarks or functions of cancer allow the cancer to survive, proliferate and disseminate and each arises at different times and in different patterns depending on the cancer type.

**[0042]** The development of cancer therapeutics which to selectively target the cancer cells while sparing normal cells dominates ongoing efforts in every area of oncology. The polynucleotides of the present invention represent such therapeutics; having the ability to selectively stabilize or destabilize cell systems, signal proliferation (survival) or death, trigger the cell cycle or senescence and/or activate or avoid the immune response depending on the cell type, e.g., cancer or normal cell.

**[0043]** According to the present invention, signal-sensor polynucleotide therapeutics may be used to destabilize the survival advantages or hallmarks of a cancer cell (hence they would be cytotoxic). In one embodiment diagnostic efforts would include the profiling of the cancer (although this would not be required *a priori*) including including metabolic state (hypoxic, acidotic), apoptotic vs. survival gene profiles, cell cycle vs. senescent stage, immune status, and stromal factors present.

**[0044]** In one embodiment the signal-sensor polynucleotide disrupts the transcriptome of the cancer cell. The disruption may affect one or more signaling or expression events. For example the encoded oncology-related polypeptide may act upstream of a transcription factor known to induce or enhance the expression of genes associated with a

cancer. Delivery of the signal-sensor polynucleotide encoding the oncology-related polypeptide which inhibits such a transcription factor (either by binding or sequestration or degradation) would thereby alter the transcriptome of the cancer cell and have a therapeutic benefit. One such transcription factor is HIF-1alpha. A signal-sensor polynucleotide encoding a protein which is capable of binding HIF-1alpha or whose expression results in lower HIF-1alpha, would effectively turn down HIF-1alpha regulated genes, e.g., VEGFA or SLC2A1, and destabilize the cancer.

**[0045]** In one embodiment, the profile of the cancer may be evaluated before the signal-sensor polynucleotide is selected. Such profiling data would inform the selection of which oncology-related polypeptide to be delivered. The profile of gene expression, categorized by hallmark class such as apoptosis, replicative capacity or metabolic signature would allow dynamic instability scoring for a polypeptide and an optimization of therapeutic window for the signal-sensor polynucleotide. As used herein, a "dynamic instability index" refers to a dose of signal-sensor polynuclotide sufficient to induce 50% increase of the oncology-related target protein *in vitro* in a cancer cell as compared to a normal matched cell.

**[0046]** Profiling may also be done within hallmark classes such as the distinction between caspase-dependent and caspase independent gene expression for the apoptosis class. Alternatively, profiling could be conducted across classes such as gene profiling of apoptosis, senescence (replicative capacity), and metabolic classes.

**[0047]** In one embodiment, the signal-sensor polynucleotides described herein may be used to reduce the expression and/or amount of a polypeptide in a cell. As a non-limiting example, MYC inhibitor A, MYC inhibitor B, MYC inhibitor C or MYC inhibitor D may be used on Hep3B cells in order to determine the potentcy of MYC inhibitor A, MYC inhibitor B, MYC inhibitor C or MYC inhibitor D at various concentrations (see e.g., Example 55).

**[0048]** In one embodiment, the signal-sensor polynucleotides described hereim may direct either cytotoxic or cytoprotective therapeutic benefit to specific cells, e.g., normal vs. cancerous.

**[0049]** In one embodiment signal-sensor polynucleotides would not only encode an oncology-related polypeptide but also a sensor sequence. Sensor sequences include, for

example, microRNA binding sites, transcription factor binding sites, artificial binding sites engineered to act as pseudo-receptors for endogenous nucleic acid binding molecules. A "sensor region" is a region of linked nucleosides of the signal-sensor polynucleotide comprising at least one sensor sequence. The signal-sensor polynucleotides of the present invention may have one or more sensor regions.

**[0050]** In one embodiment, one or more sensor regions may be located in the first flanking region. As a non-limiting example, the sensor region in the first flanking region may comprise at least one sensor sequence. The sensor sequence may be, but is not limited to, mir-122, mir-142-3p, mir-142-5p, mir-146, fragments or variants thereof. As another non-limiting example, the sensor region in the first flanking region may comprise at least one sensor sequence such as a mir-122 sequence. The mir-122 sequence may be, but is not limited to, a mir-122 binding site, mir-122 seed sequence, mir-122 binding site without the seed sequence or a combination thereof.

**[0051]** In another embodiment, one or more sensor regions may be located in the second flanking region. As a non-limiting example, the sensor region in the second flanking region may include a sensor sequence such as mir-122, mir-142-3p, mir-142-5p, mir-146, fragments or variants thereof. As another non-limiting example, the sensor region in the second flanking region may include three sensor sequences. The sensor sequences may be, but are not limited to, mir-122 sequences such as mir-122 binding sites, mir-122 seed sequences, mir-122 binding sites without the seed sequence or a combination thereof. As yet another non-limiting example, the sensor region in the second flanking region is located in the 3'UTR and the sensor region may include a sensor sequence which is a mir-122 sequence. The mir-122 sequence may be, but is not limited to, a mir-122 binding site, mir-122 seed sequence, mir-122 binding site without the seed sequence or a combination thereof.

**[0052]** In one embodiment, two or more sensor regions may be located in the same region of the signal-sensor polynucleotide such as, but not limited to, a first region first region of linked nucleotides, the first flanking region and/or the second flanking region. As a non-limiting example, the two or more sensor regions are located in the second flanking region. As yet another non-limiting example, three sensor regions are located in the 3' UTR in the second flanking region. The three sensor regions may include, mir-122

binding sites, mir-122 seed sequences, mir-122 binding sites without the seed sequence or a combination thereof

**[0053]** In another embodiment, two or more sensor regions may be located in different regions of the signal-sensor polynucleotide such as, but not limited to, the first region of linked nucleotides, the first flanking region and/or the second flanking region. As a non-limiting example, a first sensor region is located in the first flanking region and a second sensor region is located in the second flanking region. The sensor regions may comprise the same sensor sequence or different sensor sequences.

**[0054]** In one embodiment, a start codon is located within a sensor region.

**[0055]** In one embodiment, a sensor region may comprise two or more sensor sequences. The sensor sequences may be the same or different.

**[0056]** In one embodiment, the sensor region may comprise two or more sensor sequence which are different from each other but they may be based on the same mir binding site. As a non-limiting example, the sensor region may include at least one miR binding site sequence and at least one mir binding site sequence with the seed removed. As another non-limiting example, the sensor region may include at least one miR binding site sequence and at least one miR seed sequence. As yet another non-limiting example, the sensor region may include at least one miR binding site sequence with the seed removed and at least one miR seed sequence.

**[0057]** In another embodiment, the sensor region may comprise two or more sensor sequences which are in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times. In these patterns, each letter, A, B, or C represent a different miR sequence.

**[0058]** In yet another embodiment, the signal-sensor polynucleotide may include two or more sensor regions with each sensor region having one or more sensor sequences. As a non-limiting example, the sensor sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times in each of the sensor regions. As another non-limiting example, the sensor sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times across the entire signal-sensor polynucleotide. In these patterns, each letter, A, B, or C represent

a different miR sequence. As a non-limiting example, the first sensor region may have sensor sequences in the pattern ABA and the second sensor region may have sensor sequences in the pattern BAB so the overall pattern of the sensor sequences in the signal-sensor polynucleotide is ABABAB. As another non-limiting example, the first sensor region may have sensor sequences AA, the second sensor region may have sensor sequences BB, the third sensor region may have sensor sequences AA and the fourth sensor region may have sensor seuqences BB so the overall pattern of the sensor sequences in the signal-sensor polynucleotide is AABBAABB.

**[0059]** The sensor sequences in the signal-sensor polynucleotides of the present invention may include one or more regulatory sequences in the 3-UTR and/or 5'UTR of natural mRNAs, which regulate mRNA stability and translation in different tissues and cells. Such cis-regulatory elements may include, but are not limited to, Cis- RNP (Ribonucleoprotein)/RBP (RNA binding protein) regulatory elements, AU-rich element AUE, structured stem-loop, constitutive decay elements (CDEs), GC-richness and other structured mRNA motifs (Parker BJ et al., Genome Research, 2011, 21, 1929-1943, which is herein incorporated by reference in its entirety.). For example, CDEs are a class of regulatory motifs that mediate mRNA degradation through their interaction with Roquin proteins. In particular, CDEs are found in many mRNAs that encode regulators of development and inflammation to limit cytokine production in macrophage (Leppek K et al., Cell, 2013, 153, 869-881, which is herein incorporated by reference in its entirety.).

**[0060]** In one embodiment, a particular CDE can be introduced to the signal-sensor polynucleotide when the degradation of polypeptides in a cell or tissue is desired. A particular CDE can also be removed from the signal-sensor polynucleotide in order to maintain a more stable mRNA in a cell or tissue for sustaining protein expression.

**[0061]** In one embodiment, microRNA (miRNA) profiling of the cancer cells or tissues may be conducted to determine the presence or absence of miRNA in the cells or tissues to determine the appropriate microRNA to use as sensor sequences in the signal sensor polynucleotides.

**[0062]** MicroRNA gene regulation may be influenced by the sequence surrounding the microRNA such as, but not limited to, the species of the surrounding sequence, the type of sequence (e.g., heterologous, homologous and artificial), regulatory elements in the

surrounding sequence and/or structural elements in the surrounding sequence. The microRNA may be influenced by the 5'UTR and/or the 3'UTR. As a non-limiting example, a non-human 3'UTR may increase the regulatory effect of the microRNA sequence on the expression of a polypeptide of interest compared to a human 3'UTR of the same sequence type.

**[0063]** Other regulatory elements and/or structural elements of the 5'-UTR can influence microRNA mediated gene regulation. One such example is a structured IRES (Internal Ribosome Entry Site) in the 5'UTR, which is necessary for the binding of translational elongation factors to initiate protein translation. EIF4A2 binding to this secondarily structured element in the 5'UTR is necessary for microRNA mediated gene expression (Meijer HA et al., Science, 2013, 340, 82-85, herein incorporated by reference in its entirety). The sensor-signal polynucleotide can further be modified to include this structured 5'-UTR in order to enhance microRNA mediated gene regulation.

**[0064]** At least one microRNA site can be engineered into the 3' UTR of the signal-sensor polynucleotides of the present invention. In this context, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten or more microRNA sites may be engineered into the 3' UTR of the signal-sensor polynucleotides of the present invention. In one embodiment, the microRNA sites incorporated into the signal-sensor polynucleotides may be the same or may be different microRNA sites. In another embodiment, the microRNA sites incorporated into the signal-sensor polynucleotides may target the same or different tissues in the body. As a non-limiting example, through the introduction of tissue-, cell-type-,or disease-specific microRNA binding sites in the 3' UTR of a signal-sensor polynucleotide, the degree of expression in specific cell types (e.g. hepatocytes, myeloid cells, endothelial cells, cancer cells, etc.) can be reduced.

**[0065]** In one embodiment, a microRNA site can be engineered near the 5' terminus of the 3'UTR, about halfway between the 5' terminus and 3'terminus of the 3'UTR and/or near the 3'terminus of the 3'UTR. As a non-limiting example, a microRNA site may be engineered near the 5' terminus of the 3'UTR and about halfway between the 5' terminus and 3'terminus of the 3'UTR. As another non-limiting example, a microRNA site may be engineered near the 3'terminus of the 3'UTR and about halfway between the

5' terminus and 3'terminus of the 3'UTR. As yet another non-limiting example, a microRNA site may be engineered near the 5' terminus of the 3'UTR and near the 3' terminus of the 3'UTR.

**[0066]** In another embodiment, a 3'UTR can comprise 4 microRNA sites. The microRNA sites may be complete microRNA binding sites, microRNA seed sequences and/or microRNA binding site sequences without the seed sequence.

**[0067]** In one embodiment, a signal-sensor polynucleotide may be engineered to include microRNA sites which are expressed in different tissues of a subject. As a non-limiting example, a signal-sensor polynucleotide of the present invention may be engineered to include miR-192 and miR-122 to regulate expression of the signal-sensor polynucleotide in the liver and kidneys of a subject. In another embodiment, a signal-sensor polynucleotide may be engineered to include more than one microRNA sites for the same tissue. For example a signal-sensor polynucleotide of the present invention may be engineered to include miR-17-92 and miR-126 to regulate expression of the signal-sensor polynucleotide in endothelial cells of a subject.

**[0068]** In one embodiment, the therapeutic window and or differential expression associated with the oncology-related polypeptide encoded by the signal-sensor polynucleotide of the invention may be altered. For example, signal-sensor polynucleotides may be designed whereby a death signal is more highly expressed in cancer cells (or a survival signal in a normal cell) by virtue of the miRNA signature of those cells. Where a cancer cell expresses a lower level of a particular miRNA, the signal-sensor polynucleotide encoding the binding site for that miRNA (or miRNAs) would be more highly expressed. Hence, the oncology-related polypeptide encoded by the signal-sensor polynucleotide is selected as a protein which triggers or induces cell death. Neigboring noncancer cells, harboring a higher expression of the same miRNA would be less affected by the encoded death signal as the signal-sensor polynucleotide would be expressed at a lower level due to the affects of the miRNA binding to the binding site or "sensor" encoded in the 3'UTR. Conversely, cell survival or cytoprotective signals may be delivered to tissues containing cancer and non cancerous cells where a miRNA has a higher expression in the cancer cells—the result being a lower survival signal to the cancer cell and a larger survival signature to the normal cell.

Multiple signal-sensor polynucleotides may be designed and administered having different signals according to the previous paradigm.

**[0069]** In one embodiment, the expression of a signal-sensor polynucleotide may be controlled by incorporating at least one sensor sequence in the signal-sensor polynucleotide and formulating the signal-sensor polynucleotide. As a non-limiting example, a polynucleotide may be targeted to an orthotopic tumor by having a polynucleotide incorporating a miR-122 binding site and formulated in a lipid nanoparticle comprising the cationic lipid DLin-KC2-DMA (see e.g., the experiments described in Example 56A and 56B).

**[0070]** Through an understanding of the expression patterns of microRNA in different cell types, signal-sensor polynucleotides can be engineered for more targeted expression in specific cell types or only under specific biological conditions. Through introduction of tissue-specific microRNA binding sites, signal-sensor polynucleotides could be designed that would be optimal for protein expression in a tissue or in the context of a biological condition such as cancer.

**[0071]** Transfection experiments can be conducted in relevant cell lines, using engineered signal-sensor polynucleotides and protein production can be assayed at various time points post-transfection. For example, cells can be transfected with different microRNA binding site-engineering nucleic acids or signal-sensor polynucleotides and by using an ELISA kit to the relevant protein and assaying protein produced at 6 hr, 12 hr, 24 hr, 48 hr, 72 hr and 7 days post-transfection. *In vivo* experiments can also be conducted using microRNA-binding site-engineered molecules to examine changes in tissue-specific expression of formulated signal-sensor polynucleotides.

**[0072]** In one embodiment, the signal-sensor polynucleotides of the invention may include at least one microRNA in order to dampen the antigen presentation by antigen presenting cells. The microRNA may be the complete microRNA sequence, the microRNA seed sequence, the microRNA sequence without the seed or a combination thereof. As a non-limiting example, the microRNA incorporated into the signal-sensor polynucleotide may be specific to the hematopoietic system. As another non-limiting example, the microRNA incorporated into the signal-sensor polynucleotides of the invention to dampen antigen presentation is miR-142-3p.

**[0073]** In one embodiment, the signal-sensor polynucleotides of the invention may include at least one microRNA in order to dampen expression of the encoded polypeptide in a cell of interest. As a non-limiting example, the signal-sensor polynucleotides of the invention may include at least one miR-122 binding site in order to dampen expression of an encoded polypeptide of interest in the liver. As another non-limiting example, the signal-sensor polynucleotides of the invention may include at least one miR-142-3p binding site, miR-142-3p seed sequence, miR-142-3p binding site without the seed, miR-142-5p binding site, miR-142-5p seed sequence, miR-142-5p binding site without the seed, miR-146 binding site, miR-146 seed sequence and/or miR-146 binding site without the seed sequence (see e.g., the experiment outlined in Example 47 and Example 60).

**[0074]** According to the present invention, the signal-sensor polynucleotides described herein may be modified as to avoid the deficiencies of other polypeptide-encoding molecules of the art. Hence, in this embodiment the signal-sensor polynucleotides are referred to as modified signal-sensor polynucleotides or primary constructs, modified mRNA or mmRNA.

**[0075]** Provided herein, in part, are signal-sensor polynucleotide polynucleotides, primary constructs and/or mmRNA encoding oncology-related polypeptides of interest which have been designed to improve one or more of the stability and/or clearance in tissues, receptor uptake and/or kinetics, cellular access by the compositions, engagement with translational machinery, mRNA half-life, translation efficiency, immune evasion, protein production capacity, secretion efficiency (when applicable), accessibility to circulation, protein half-life and/or modulation of a cell's status, function and/or activity.

## I. Compositions of the Invention

**[0076]** The present invention provides nucleic acid molecules, specifically signal-sensor polynucleotides, primary constructs and/or mmRNA which encode one or more oncology-related polypeptides of interest. Specifically the invention contemplates signal-sensor polynucleotides which are useful in cancer or cancer related diseases, disorders. As used herein, "signal-sensor polynucleotides" are nucleic acid transcripts which encode one or more oncology-related polypeptides of interest that, when translated, delivers a "signal" to the cell (cancer or noncancerous) which results in the therapeutic benefit to the organism of either being detrimental to the cancer cell or beneficial to normal cells or

both detrimental to cancer cells and advantageous to normal cells. The signal-sensor polynucleotides may optionally further comprise a sequence (translatable or not) which "senses" the microenvironment of the polynucleotide and alters (a) the function or phenotypic outcome associated with the peptide or protein which is translated, (b) the expression level of the signal-sensor polynucleotide, and/or both.

**[0077]** The term "nucleic acid," in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides. These polymers are often referred to as polynucleotides. Exemplary nucleic acids or polynucleotides of the invention include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β- D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2′-amino-LNA having a 2′-amino functionalization, and 2′-amino- α-LNA having a 2′-amino functionalization) or hybrids thereof.

**[0078]** In preferred embodiments, the signal-sensor polynucleotide or nucleic acid molecule is a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro, in vivo, in situ* or *ex vivo*. Signal-sensor polynucleotides of the invention may be mRNA or any nucleic acid molecule and may or may not be chemically modified.

**[0079]** Traditionally, the basic components of an mRNA molecule include at least a coding region, a 5′UTR, a 3′UTR, a 5′ cap and a poly-A tail. Building on this wild type modular structure, the present invention expands the scope of functionality of traditional mRNA molecules by providing signal-sensor polynucleotides or primary RNA constructs which maintain a modular organization, but which comprise one or more structural and/or chemical modifications or alterations which impart useful properties to the polynucleotide including, in some embodiments, the lack of a substantial induction of the innate immune response of a cell into which the signal-sensor polynucleotide is introduced. As such, modified mRNA molecules of the present invention, which may be synthetic, are termed "mmRNA." As used herein, a "structural" feature or modification is one in which two or more linked nucleotides are inserted, deleted, duplicated, inverted or

randomized in a signal-sensor polynucleotide polynucleotide, primary construct or mmRNA without significant chemical modification to the nucleotides themselves. Because chemical bonds will necessarily be broken and reformed to effect a structural modification, structural modifications are of a chemical nature and hence are chemical modifications. However, structural modifications will result in a different sequence of nucleotides. For example, the polynucleotide "ATCG" may be chemically modified to "AT-5meC-G". The same polynucleotide may be structurally modified from "ATCG" to "ATCCCG". Here, the dinucleotide "CC" has been inserted, resulting in a structural modification to the polynucleotide.

Signal-sensor polynucleotide, primary construct or mmRNA Architecture

**[0080]** The signal-sensor polynucleotides of the present invention are distinguished from wild type mRNA in their functional and/or structural design features which serve to, as evidenced herein, overcome existing problems of effective polypeptide production using nucleic acid-based therapeutics.

**[0081]** Figure 1 shows a representative signal-sensor primary construct **100** of the present invention. As used herein, the term "primary construct" or "primary mRNA construct" refers to a signal-sensor polynucleotide transcript which encodes one or more polypeptides of interest and which retains sufficient structural and/or chemical features to allow the polypeptide of interest encoded therein to be translated. Signal-sensor primary constructs may be polynucleotides of the invention. When structurally or chemically modified, the signal-sensor primary construct may be referred to as a mmRNA.

**[0082]** Returning to FIG. **1**, the primary construct **100** here contains a first region of linked nucleotides **102** that is flanked by a first flanking region **104** and a second flaking region **106**. As used herein, the "first region" may be referred to as a "coding region" or "region encoding" or simply the "first region." This first region may include, but is not limited to, the encoded oncology-related polypeptide of interest. The oncology-related polypeptide of interest may comprise at its 5' terminus one or more signal peptide sequences encoded by a signal peptide sequence region **103**. The flanking region **104** may comprise a region of linked nucleotides comprising one or more complete or incomplete 5′ UTRs sequences. The flanking region **104** may also comprise a 5′ terminal cap **108**. The second flanking region **106** may comprise a region of linked nucleotides

comprising one or more complete or incomplete 3′ UTRs. The flanking region **106** may also comprise a 3′ tailing sequence **110** and a 3'UTR **120**.

**[0083]** Bridging the 5′ terminus of the first region **102** and the first flanking region **104** is a first operational region **105**. Traditionally this operational region comprises a start codon. The operational region may alternatively comprise any translation initiation sequence or signal including a start codon.

**[0084]** Bridging the 3′ terminus of the first region **102** and the second flanking region **106** is a second operational region **107**. Traditionally this operational region comprises a stop codon. The operational region may alternatively comprise any translation initiation sequence or signal including a stop codon. According to the present invention, multiple serial stop codons may also be used. In one embodiment, the operation region of the present invention may comprise two stop codons. The first stop codon may be "TGA" and the second stop codon may be selected from the group consisting of "TAA," "TGA" and "TAG." The operation region may further comprise three stop codons. The third stop codon may be selected from the group consisting of "TAA," "TGA" and "TAG."

**[0085]** Turning to Figure **2**, the 3'UTR **120** of the second flanking region **106** may comprise one or more sensor sequences **130**. A region comprising at least one sensor sequence is referred to as a "sensor region." These sensor sequences as discussed herein operate as pseudo-receptors (or binding sites) for ligands of the local microenvironment of the primary construct or signal-sensor polynucleotide. For example, microRNA bindng sites or miRNA seeds may be used as sensors such that they function as pseudoreceptors for any microRNAs present in the environment of the polynucleotide.

**[0086]** Generally, the shortest length of the first region of the signal-sensor primary construct of the present invention can be the length of a nucleic acid sequence that is sufficient to encode for a dipeptide, a tripeptide, a tetrapeptide, a pentapeptide, a hexapeptide, a heptapeptide, an octapeptide, a nonapeptide, or a decapeptide. In another embodiment, the length may be sufficient to encode a peptide of 2-30 amino acids, e.g. 5-30, 10-30, 2-25, 5-25, 10-25, or 10-20 amino acids. The length may be sufficient to encode for a peptide of at least 11, 12, 13, 14, 15, 17, 20, 25 or 30 amino acids, or a peptide that is no longer than 40 amino acids, e.g. no longer than 35, 30, 25, 20, 17, 15,

14, 13, 12, 11 or 10 amino acids. Examples of dipeptides that the polynucleotide sequences can encode or include, but are not limited to, carnosine and anserine.

**[0087]** Generally, the length of the first region encoding the oncology-related polypeptide of interest of the present invention is greater than about 30 nucleotides in length (e.g., at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides). As used herein, the "first region" may be referred to as a "coding region" or "region encoding" or simply the "first region."

**[0088]** In some embodiments, the signal-sensor polynucleotide polynucleotide, primary construct, or mmRNA includes from about 30 to about 100,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to 70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000).

**[0089]** According to the present invention, the first and second flanking regions may range independently from 15-1,000 nucleotides in length (e.g., greater than 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600,

700, 800, and 900 nucleotides or at least 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, and 1,000 nucleotides).

**[0090]** According to the present invention, the tailing sequence may range from absent to 500 nucleotides in length (e.g., at least 60, 70, 80, 90, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, or 500 nucleotides). Where the tailing region is a polyA tail, the length may be determined in units of or as a function of polyA binding protein binding. In this embodiment, the polyA tail is long enough to bind at least 4 monomers of polyA binding protein. PolyA binding protein monomers bind to stretches of approximately 38 nucleotides. As such, it has been observed that polyA tails of about 80 nucleotides and 160 nucleotides are functional.

**[0091]** According to the present invention, the capping region may comprise a single cap or a series of nucleotides forming the cap. In this embodiment the capping region may be from 1 to 10, e.g. 2-9, 3-8, 4-7, 1-5, 5-10, or at least 2, or 10 or fewer nucleotides in length. In some embodiments, the cap is absent.

**[0092]** According to the present invention, the first and second operational regions may range from 3 to 40, e.g., 5-30, 10-20, 15, or at least 4, or 30 or fewer nucleotides in length and may comprise, in addition to a start and/or stop codon, one or more signal and/or restriction sequences.

*Cyclic signal-sensor polynucleotides*

**[0093]** According to the present invention, a signal-sensor primary construct or mmRNA may be cyclized, or concatemerized, to generate a translation competent molecule to assist interactions between poly-A binding proteins and 5′-end binding proteins. The mechanism of cyclization or concatemerization may occur through at least 3 different routes: 1) chemical, 2) enzymatic, and 3) ribozyme catalyzed. The newly formed 5′-/3′-linkage may be intramolecular or intermolecular.

**[0094]** In the first route, the 5′-end and the 3′-end of the nucleic acid may contain chemically reactive groups that, when close together, form a new covalent linkage between the 5′-end and the 3′-end of the molecule. The 5′-end may contain an NHS-ester reactive group and the 3′-end may contain a 3′-amino-terminated nucleotide such that in an organic solvent the 3′-amino-terminated nucleotide on the 3′-end of a synthetic mRNA

molecule will undergo a nucleophilic attack on the 5′-NHS-ester moiety forming a new 5′-/3′-amide bond.

**[0095]** In the second route, T4 RNA ligase may be used to enzymatically link a 5′-phosphorylated nucleic acid molecule to the 3′-hydroxyl group of a nucleic acid forming a new phosphorodiester linkage. In an example reaction, 1μg of a nucleic acid molecule is incubated at 37°C for 1 hour with 1-10 units of T4 RNA ligase (New England Biolabs, Ipswich, MA) according to the manufacturer's protocol. The ligation reaction may occur in the presence of a split oligonucleotide capable of base-pairing with both the 5′- and 3′-region in juxtaposition to assist the enzymatic ligation reaction.

**[0096]** In the third route, either the 5′-or 3′-end of the cDNA template encodes a ligase ribozyme sequence such that during *in vitro* transcription, the resultant nucleic acid molecule can contain an active ribozyme sequence capable of ligating the 5′-end of a nucleic acid molecule to the 3′-end of a nucleic acid molecule. The ligase ribozyme may be derived from the Group I Intron, Group I Intron, Hepatitis Delta Virus, Hairpin ribozyme or may be selected by SELEX (systematic evolution of ligands by exponential enrichment). The ribozyme ligase reaction may take 1 to 24 hours at temperatures between 0 and 37°C.

*Signal-Sensor Polynucleotide Multimers*

**[0097]** According to the present invention, multiple distinct signal-sensor polynucleotides, primary constructs or mmRNA may be linked together through the 3′-end using nucleotides which are modified at the 3′-terminus. Chemical conjugation may be used to control the stoichiometry of delivery into cells. For example, the glyoxylate cycle enzymes, isocitrate lyase and malate synthase, may be supplied into HepG2 cells at a 1:1 ratio to alter cellular fatty acid metabolism. This ratio may be controlled by chemically linking signal-sensor polynucleotides, primary constructs or mmRNA using a 3′-azido terminated nucleotide on one signal-sensor polynucleotide, primary construct or mmRNA species and a C5-ethynyl or alkynyl-containing nucleotide on the opposite signal-sensor polynucleotide, primary construct or mmRNA species. The modified nucleotide is added post-transcriptionally using terminal transferase (New England Biolabs, Ipswich, MA) according to the manufacturer's protocol. After the addition of the 3′-modified nucleotide, the two signal-sensor polynucleotide, primary construct or

mmRNA species may be combined in an aqueous solution, in the presence or absence of copper, to form a new covalent linkage via a click chemistry mechanism as described in the literature.

**[0098]** In another example, more than two signal-sensor polynucleotides may be linked together using a functionalized linker molecule. For example, a functionalized saccharide molecule may be chemically modified to contain multiple chemical reactive groups (SH-, $NH_2$-, $N_3$, etc…) to react with the cognate moiety on a 3′-functionalized signal-sensorpolynucleotide molecule (i.e., a 3′-maleimide ester, 3′-NHS-ester, alkynyl). The number of reactive groups on the modified saccharide can be controlled in a stoichiometric fashion to directly control the stoichiometric ratio of conjugated signal-sensor polynucleotide, primary construct or mmRNA.

*Signal-sensor polynucleotide Conjugates and Combinations*

**[0099]** In order to further enhance oncology-related protein production, signal-sensor polynucleotide primary constructs or mmRNA of the present invention can be designed to be conjugated to other polynucleotides, oncology-related polypeptides, dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases, proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell, hormones and hormone receptors, non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, or a drug.

**[00100]** Conjugation may result in increased stability and/or half life and may be particularly useful in targeting the signal-sensor polynucleotides, primary constructs or mmRNA to specific sites in the cell, tissue or organism.

**[00101]** According to the present invention, the signal-sensor polynucleotide mmRNA or primary constructs may be administered with, or further encode one or more of RNAi agents, siRNAs, shRNAs, miRNAs, miRNA binding sites, antisense RNAs, ribozymes,

catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers or vectors, and the like.

**[00102]** In one embodiment, the signal-sensor polynucleotides described herein may be conjugated with a moiety to target various cancer cells such as, but not limited to, the moieties described in US Patent Application No. US20130216561, the contents of which are herein incorporated by reference in its entirety. The linkage between the signal-sensor polynucleotides and the cancer targeting moiety may be an acid cleavable linkage that can increase the efficacy of the conjugate such as, but not limited to, the linkages described in US Patent Application No. US20130216561, the contents of which are herein incorporated by reference in its entirety.

*Bifunctional signal-sensor polynucleotide*

**[00103]** In one embodiment of the invention are bifunctional signal-sensor polynucleotides (e.g., bifunctional primary constructs or bifunctional mmRNA). As the name implies, bifunctional signal-sensor polynucleotides are those having or capable of at least two functions. These molecules may also by convention be referred to as multi-functional.

**[00104]** The multiple functionalities of bifunctional signal-sensor polynucleotides may be encoded by the RNA (the function may not manifest until the encoded product is translated) or may be a property of the polynucleotide itself. It may be structural or chemical. Bifunctional modified signal-sensor polynucleotides may comprise a function that is covalently or electrostatically associated with the polynucleotides. Further, the two functions may be provided in the context of a complex of a signal-sensor polynucleotide and another molecule.

**[00105]** Bifunctional signal-sensor polynucleotides may encode oncology-related peptides which are anti-proliferative. These peptides may be linear, cyclic, constrained or random coil. They may function as aptamers, signaling molecules, ligands or mimics or mimetics thereof. Anti-proliferative peptides may, as translated, be from 3 to 50 amino acids in length. They may be 5-40, 10-30, or approximately 15 amino acids long. They may be single chain, multichain or branched and may form complexes, aggregates or any multi-unit structure once translated.

*Noncoding Signal-Sensor Polynucleotides*

**[00106]** As described herein, provided are signal-sensor polynucleotides and primary constructs having sequences that are partially or substantially not translatable, e.g., having a noncoding region. Such noncoding region may be the "first region" of the signal-sensor primary construct. Alternatively, the noncoding region may be a region other than the first region. Such molecules are generally not translated, but can exert an effect on protein production by one or more of binding to and sequestering one or more translational machinery components such as a ribosomal protein or a transfer RNA (tRNA), thereby effectively reducing protein expression in the cell or modulating one or more pathways or cascades in a cell which in turn alters protein levels. The signal-sensor polynucleotide and/or primary construct may contain or encode one or more long noncoding RNA (lncRNA, or lincRNA) or portion thereof, a small nucleolar RNA (sno-RNA), micro RNA (miRNA), small interfering RNA (siRNA) or Piwi-interacting RNA (piRNA).

*Auxotrophic Signal-Sensor Polynucleotides*

**[00107]** In one embodiment, the signal-sensor polynucleotides of the present invention may be auxotrophic. As used herein, the term "auxotrophic" refers to signal-sensor polynucleotides that comprise at least one feature that triggers, facilitates or induces the degradation or inactivation of the itself in response to spatial or temporal cues such that oncology-related protein expression is substantially prevented or reduced. Such spatial or temporal cues include the location of the signal-sensor polynucleotide to be translated such as a particular tissue or organ or cellular environment. Also contemplated are cues involving temperature, pH, ionic strength, moisture content, and the like.

**[00108]** In one embodiment, the feature is located in a terminal region of the signal-sensor polynucleotides of the present invention. As a non-limiting example, the auxotrophic mRNA may contain a miR binding site in the terminal region which binds to a miR expressed in a selected tissue so that the expression of the auxotrophic mRNA is substantially prevented or reduced in the selected tissue. To this end and for example, an auxotrophic mRNA containing a miR-122 binding site will not produce protein if localized to the liver since miR-122 is expressed in the liver and binding of the miR would effectuate destruction of the auxotrophic mRNA. As a non-limiting example, HEK293 cells do not express miR-122 so there would be little to no downregulation of a

signal-sensor polynucleotide having a miR-122 sequence in HEK293 but for hepatocytes which do expression miR-122 there would be a downregulation of a signal-sensor polynucleotide having a miR-122 sequence in hepatocytes (see e.g., the study outlined Example 19). As another non-limiting example, the miR-122 level can be measured in HeLa cells, primary human hepatocytes and primary rat hepatocytes prior to administration with a signal-sensor polynucleotide encoding having at least one miR-122 binding site, miR-122 binding site without the seed sequence or a miR-122 binding site After administration the expression of the signal-sensor polynucleotide can be measured to determine the dampening effect of the miR-122 in the signal-sensor polynucleotide (see e.g., the studies outlined in Examples 41, 42, 43 57, 58 and 59). As yet another non-limiting example, the effectiveness of the miR-122 binding site, miR-122 seed or the miR-122 binding site without the seed in different 3'UTRs may be evaluated in order to determine the proper UTR for the desired outcome such as, but not limited to, the highest dampening effect (see e.g., the study outlined in Example 46).

**[00109]** In one embodiment, the degradation or inactivation of auxotrophic mRNA may comprise a feature responsive to a change in pH. As a non-limiting example, the auxotrophic mRNA may be triggered in an environment having a pH of between pH 4.5 to 8.0 such as at a pH of 5.0 to 6.0 or a pH of 6.0 to 6.5. The change in pH may be a change of 0.1 unit, 0.2 units, 0.3 units, 0.4 units, 0.5 units, 0.6 units, 0.7 units, 0.8 units, 0.9 units, 1.0 units, 1.1 units, 1.2 units, 1.3 units, 1.4 units, 1.5 units, 1.6 units, 1.7 units, 1.8 units, 1.9 units, 2.0 units, 2.1 units, 2.2 units, 2.3 units, 2.4 units, 2.5 units, 2.6 units, 2.7 units, 2.8 units, 2.9 units, 3.0 units, 3.1 units, 3.2 units, 3.3 units, 3.4 units, 3.5 units, 3.6 units, 3.7 units, 3.8 units, 3.9 units, 4.0 units or more.

**[00110]** In another embodiment, the degradation or inactivation of auxotrophic mRNA may be triggered or induced by changes in temperature. As a non-limiting example, a change of temperature from room temperature to body temperature. The change of temperature may be less than 1°C, less than 5°C, less than 10°C, less than 15°C, less than 20°C, less than 25°C or more than 25°C.

**[00111]** In yet another embodiment, the degradation or inactivation of auxotrophic mRNA may be triggered or induced by a change in the levels of ions in the subject. The

ions may be cations or anions such as, but not limited to, sodium ions, potassium ions, chloride ions, calcium ions, magnesium ions and/or phosphate ions.

**[00112]**

Oncology-related polypeptides of interest

**[00113]** According to the present invention, the signal-sensor primary construct is designed to encode one or more oncology-related polypeptides of interest or fragments thereof. An oncology-related polypeptide of interest may include, but is not limited to, whole polypeptides, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, a plurality of nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, the term "oncology-related polypeptides of interest" refers to any polypeptide which is selected to be encoded in the signal-sensor primary construct of the present invention. As used herein, "polypeptide" means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides such as antibodies or insulin and may be associated or linked. Most commonly disulfide linkages are found in multichain polypeptides. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

**[00114]** The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence,

and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

**[00115]** In some embodiments "variant mimics" are provided. As used herein, the term "variant mimic" is one which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoro-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

**[00116]** "Homology" as it applies to amino acid sequences is defined as the percentage of residues in the candidate amino acid sequence that are identical with the residues in the amino acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Methods and computer programs for the alignment are well known in the art. It is understood that homology depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation.

**[00117]** By "homologs" as it applies to polypeptide sequences means the corresponding sequence of other species having substantial identity to a second sequence of a second species.

**[00118]** "Analogs" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

**[00119]** The present invention contemplates several types of compositions which are polypeptide based including variants and derivatives. These include substitutional, insertional, deletion and covalent variants and derivatives. The term "derivative" is used synonymously with the term "variant" but generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or starting molecule.

**[00120]** As such, signal-sensor polynucleotides encoding oncology-related polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference sequences, in particular the oncology-related polypeptide sequences disclosed herein, are included within the scope of this invention. For example,

sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences of the invention (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

**[00121]** "Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

**[00122]** As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

**[00123]** "Insertional variants" when referring to polypeptides are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a

native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

**[00124]** "Deletional variants" when referring to polypeptides are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

**[00125]** "Covalent derivatives" when referring to polypeptides include modifications of a native or starting protein with an organic proteinaceous or non-proteinaceous derivatizing agent, and/or post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

**[00126]** Certain post-translational modifications are the result of the action of recombinant host cells on the expressed oncology-related polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in the oncology-related polypeptides produced in accordance with the present invention.

**[00127]** Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

**[00128]** "Features" when referring to polypeptides are defined as distinct amino acid sequence-based components of a molecule. Features of the polypeptides encoded by the mmRNA of the present invention include surface manifestations, local conformational

shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

**[00129]** As used herein when referring to polypeptides the term "surface manifestation" refers to a polypeptide based component of a protein appearing on an outermost surface.

**[00130]** As used herein when referring to polypeptides the term "local conformational shape" means a polypeptide based structural manifestation of a protein which is located within a definable space of the protein.

**[00131]** As used herein when referring to polypeptides the term "fold" refers to the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include domains and regions formed due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

**[00132]** As used herein the term "turn" as it relates to protein conformation means a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

**[00133]** As used herein when referring to polypeptides the term "loop" refers to a structural feature of a polypeptide which may serve to reverse the direction of the backbone of a peptide or polypeptide. Where the loop is found in a polypeptide and only alters the direction of the backbone, it may comprise four or more amino acid residues. Oliva et al. have identified at least 5 classes of protein loops (J. Mol Biol 266 (4): 814-830; 1997). Loops may be open or closed. Closed loops or "cyclic" loops may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids between the bridging moieties. Such bridging moieties may comprise a cysteine-cysteine bridge (Cys-Cys) typical in polypeptides having disulfide bridges or alternatively bridging moieties may be non-protein based such as the dibromozylyl agents used herein.

**[00134]** As used herein when referring to polypeptides the term "half-loop" refers to a portion of an identified loop having at least half the number of amino acid resides as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to comprise an odd number of amino acids, a half-loop of the odd-numbered

loop will comprise the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a loop identified as a 7 amino acid loop could produce half-loops of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4).

**[00135]** As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

**[00136]** As used herein when referring to polypeptides the term "half-domain" means a portion of an identified domain having at least half the number of amino acid resides as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

**[00137]** As used herein when referring to polypeptides the terms "site" as it pertains to amino acid based embodiments is used synonymously with "amino acid residue" and "amino acid side chain." A site represents a position within a peptide or polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present invention.

**[00138]** As used herein the terms "termini" or "terminus" when referring to polypeptides refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids

in the terminal regions. The polypeptide based molecules of the present invention may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the invention are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

**[00139]** Once any of the features have been identified or defined as a desired component of a polypeptide to be encoded by the signal-sensor primary construct or mmRNA of the invention, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules of the invention. For example, a manipulation which involved deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

**[00140]** Modifications and manipulations can be accomplished by methods known in the art such as, but not limited to, site directed mutagenesis. The resulting modified molecules may then be tested for activity using *in vitro* or *in vivo* assays such as those described herein or any other suitable screening assay known in the art.

**[00141]** According to the present invention, the oncology-related polypeptides may comprise a consensus sequence which is discovered through rounds of experimentation. As used herein a "consensus" sequence is a single sequence which represents a collective population of sequences allowing for variability at one or more sites.

**[00142]** As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of oncology-related polypeptides of interest of this invention. For example, provided herein is any protein fragment (meaning an oncology-related polypeptide sequence at least one amino acid residue shorter than a reference oncology-related polypeptide sequence but

otherwise identical) of a reference oncology-related protein 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or greater than 100 amino acids in length. In another example, any oncology-related protein that includes a stretch of about 20, about 30, about 40, about 50, or about 100 amino acids which are about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or about 100% identical to any of the sequences described herein can be utilized in accordance with the invention. In certain embodiments, a polypeptide to be utilized in accordance with the invention includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided or referenced herein.

Encoded Oncology-Related Polypeptides

**[00143]** The signal-sensor primary constructs or mmRNA of the present invention may be designed to encode oncology-related polypeptides of interest such as oncology-related peptides and proteins.

**[00144]** In one embodiment, signal-sensor primary constructs or mmRNA of the present invention may encode variant polypeptides which have a certain identity with a reference oncology-related polypeptide sequence. As used herein, a "reference oncology-related polypeptide sequence" refers to a starting oncology-related polypeptide sequence. Reference sequences may be wild type sequences or any sequence to which reference is made in the design of another sequence. A "reference polypeptide sequence" may, e.g., be any one of the protein sequence listed in Table 6.

**[00145]** The term "identity" as known in the art, refers to a relationship between the sequences of two or more peptides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between peptides, as determined by the number of matches between strings of two or more amino acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., "algorithms"). Identity of related peptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular

Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo et al., SIAM J. Applied Math. 48, 1073 (1988).

**[00146]** In some embodiments, the polypeptide variant may have the same or a similar activity as the reference oncology-related polypeptide. Alternatively, the variant may have an altered activity (e.g., increased or decreased) relative to a reference oncology-related polypeptide. Generally, variants of a particular signal-sensor polynucleotide or oncology-related polypeptide of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference signal-sensor polynucleotide or oncology-related polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.) Other tools are described herein, specifically in the definition of "identity."

**[00147]** Default parameters in the BLAST algorithm include, for example, an expect threshold of 10, Word size of 28, Match/Mismatch Scores 1, -2, Gap costs Linear. Any filter can be applied as well as a selection for species specific repeats, e.g., Homo sapiens.

**[00148]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may be used to treat a disease, disorder and/or condition in a subject.

**[00149]** In one embodiment, the polynucleotides, primary constructs and/or mmRNA may be used to reduce, eliminate or prevent tumor growth in a subject.

**[00150]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may be used to recude and/or ameliorate at least one symptom of cancer in a subject. A symptom of cancer may include, but is not limited to, weakness, aches and pains, fever, fatigue, weight loss, blood clots, increased blood calcium levels, low white blood cell count, short of breath, dizziness, headaches, hyperpigmentation, jaundice, erthema, pruritis, excessive hair growth, change in bowel habits, change in bladder function, long-lasting sores, white patches inside the mouth, white spots on the

tongue, unusual bleeding or discharge, thickening or lump on parts of the body, indigestion, trouble swallowing, changes in warts or moles, change in new skin and nagging cough or hoarseness. Further, the signal-sensor polynucleotides, primary constructs and/or mmRNA may reduce a side-effect associated with cancer such as, but not limited to, chemo brain, peripheral neuropathy, fatigue, depression, nausea, vomiting, pain, anemia, lymphedema, infections, sexual side effects, reduced fertility or infertility, ostomics, insomnia and hair loss.

*Oncology-related proteins or oncology-related peptides*

**[00151]** The signal-sensor primary constructs or mmRNA disclosed herein, may encode one or more validated or "in testing" oncology-related proteins or oncology-related peptides.

**[00152]** According to the present invention, one or more oncology-related proteins or oncology-related peptides currently being marketed or in development may be encoded by the oncology-related signal-sensor polynucleotide, primary constructs or mmRNA of the present invention. While not wishing to be bound by theory, it is believed that incorporation into the signal-sensor primary constructs or mmRNA of the invention will result in improved therapeutic efficacy due at least in part to the specificity, purity and selectivity of the construct designs.

**[00153]** The signal-sensor polynucleotides, primary constructs and/or mmRNA may alter a biological and/or physiolocial process and/or compound such as, but not limited to, the cell cycle, the DNA damage response (e.g., DNA damage repair), apoptosis, angiogenesis, cell motility, the epithelial to mesenchymal transition in epithelial cells, the phosphatidyl inositol 3 (PI3) kinase/Akt cellular signaling pathway, telomerase activity and/or expression, tumor metastasis, tumorigenesis, cathepsins, cell senescence, receptor tyrosine kinase signaling, metabolism and drug metabolism, G protein signaling, growth factors and receptors, heat shock proteins, histone deacetylases, hormone receptors, hypoxia, poly ADP-ribose polymerases, protein kinases, RAS signaling, topisomerases, transcription factors and tumor suppressor activity in cancerous, precancerous and/or other cells.

**[00154]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may used to express a polypeptide in cells or tissues for the purpose of replacing the protein produced from a deleted or mutated gene.

**[00155]** Further, the polynucleotides, primary constructs or mmRNA of the invention may be used to treat cancer which has been caused by carcinogens of natural and/or synthetic origin. In another embodiment, the use of the polynucleotides, primary constructs and/or mmRNA may be used to treat cancer caused by other organisms and/or cancers caused by viral infection.

Sensors in the flanking regions: Untranslated Regions (UTRs)

**[00156]** Untranslated regions (UTRs) of a gene are transcribed but not translated. The 5′UTR starts at the transcription start site and continues to the start codon but does not include the start codon; whereas, the 3′UTR starts immediately following the stop codon and continues until the transcriptional termination signal. There is growing body of evidence about the regulatory roles played by the UTRs in terms of stability of the nucleic acid molecule and translation. The regulatory features of a UTR can be incorporated into the signal-sensor polynucleotides, primary constructs and/or mmRNA of the present invention to enhance the stability of the molecule. The specific features can also be incorporated to ensure controlled down-regulation of the transcript in case they are misdirected to undesired organs sites. The untranslated regions may be incorporated into a vector system which can produce mRNA and/or be delivered to a cell, tissue and/or organism to produce a polypeptide of interest.

**[00157]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA of the present may comprise at least one terminal modification. Non-limiting examples of terminal modifications are described in US Provisional Patent Application No US 61/729,933, filed November 26, 2012, entitled Terminally Optimized Modified RNAs, US Provisional Patent application No US 61/737,224, filed December 14, 2012, entitled Terminally Optimized RNAs, US Provisional Patent Application No US 61/758,921, filed January 31, 2013, entitled Differential Targeting Using RNA Constructs, US Provisional Patent Application No. US 61/781,139, filed March 14, 2013, entitled Differential Targeting Using RNA Constructs, US Provisional Patent Application No US 61/829,359, filed May 31, 2013, entitled Differential Targeting Using

RNA Constructs, US Provisional Patent Application No. 61/839,903, filed June 27, 2013, entitled Differential Targeting Using RNA Constructs, US Provisional Patent Application No. 61/842,709, filed July 3, 2013, entitled Differential Targeting Using RNA Constructs, and US Provisional Patent Application No. 61/857,436, filed July 23, 2013, entitled Differential Targeting Using RNA Constructs, the contents of each of which are herein incorporated by reference in their entireties. These terminal modifications include, but are not limited to, 5'caps, microRNA binding sites in the terminal region, chain terminating nucleosides, translation enhancer elements in the terminal region and tailing sequences including a polyA-G quartet and stem loop sequences.

*5' UTR and Translation Initiation*

**[00158]** Natural 5′UTRs bear features which play roles in for translation initiation. They harbor signatures like Kozak sequences which are commonly known to be involved in the process by which the ribosome initiates translation of many genes. Kozak sequences have the consensus CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another 'G'. 5′UTR also have been known to form secondary structures which are involved in elongation factor binding. For example, one of the secondary 5'-UTR structures is the structured IRES for eIF4A2 elongation factor binding, which is necessary for the microRNA mediated gene repression at 3'-UTR.

**[00159]** 5'UTR secondary structures involved in elongation factor binding can interact with other RNA binding molecules in the 5'UTR or 3'UTR to regulate gene expression. For example, the elongation factor EIF4A2 binding to a secondarily structured element in the 5'UTR is necessary for microRNA mediated repression (Meijer HA et al., Science, 2013, 340, 82-85, herein incorporated by reference in its entirety). The different secondary structures in the 5'UTR can be incorporated into the flanking region to either stabilize or selectively destalized mRNAs in specific tissues or cells.

**[00160]** By engineering the features typically found in abundantly expressed genes of specific target organs, one can enhance the stability and oncology-related protein production of the signal-sensor polynucleotides, primary constructs or mmRNA of the invention. For example, introduction of 5′ UTR of liver-expressed mRNA, such as albumin, serum amyloid A, Apolipoprotein A/B/E, transferrin, alpha fetoprotein,

erythropoietin, or Factor VIII, could be used to enhance expression of a nucleic acid molecule, such as a mmRNA, in hepatic cell lines or liver. Likewise, use of 5′ UTR from other tissue-specific mRNA to improve expression in that tissue is possible – for muscle (MyoD, Myosin, Myoglobin, Myogenin, Herculin), for endothelial cells (Tie-1, CD36), for myeloid cells (C/EBP, AML1, G-CSF, GM-CSF, CD11b, MSR, Fr-1, i-NOS), for leukocytes (CD45, CD18), for adipose tissue (CD36, GLUT4, ACRP30, adiponectin) and for lung epithelial cells (SP-A/B/C/D).

**[00161]** Other non-UTR sequences may be incorporated into the 5′ (or 3′ UTR) UTRs. For example, introns or portions of introns sequences may be incorporated into the flanking regions of the signal-sensor polynucleotides, primary constructs or mmRNA of the invention. Incorporation of intronic sequences may increase protein production as well as mRNA levels.

*Translation Enhancer Elements (TEEs)*

**[00162]** In one embodiment, the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA may include at least one translational enhancer polynucleotide, translation enhancer element, translational enhancer elements (collectively referred to as "TEE"s). As a non-limiting example, the TEE may be located between the transcription promoter and the start codon. The signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA with at least one TEE in the 5'UTR may include a cap at the 5'UTR. Further, at least one TEE may be located in the 5'UTR of signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA undergoing cap-dependent or cap-independent translation.

**[00163]** The term "translational enhancer element" or "translation enhancer element" (herein collectively referred to as "TEE") refers to sequences that increase the amount of polypeptide or protein produced from an mRNA.

**[00164]** In one embodiment, TEEs are conserved elements in the UTR which can promote translational activity of a nucleic acid such as, but not limited to, cap-dependent or cap-independent translation. The conservation of these sequences has been previously shown by Panek et al (Nucleic Acids Research, 2013, 1-10; herein incorporated by reference in its entirety) across 14 species including humans.

**[00165]** In one embodiment, the TEE may be any of the TEEs listed in Table 35 in Example 45, including portion and/or fragments thereof. The TEE sequence may include at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or more than 99% of the TEE sequences disclosed in Table 35 and/or the TEE sequence may include a 5-30 nucleotide fragment, a 5-25 nucleotide fragment, a 5-20 nucleotide fragment, a 5-15 nucleotide fragment, a 5-10 nucleotide fragment of the TEE sequences disclosed in Table 35.

**[00166]** In one non-limiting example, the TEEs known may be in the 5′-leader of the Gtx homeodomain protein (Chappell et al., Proc. Natl. Acad. Sci. USA 101:9590-9594, 2004, herein incorporated by reference in their entirety).

**[00167]** In another non-limiting example, TEEs are disclosed as SEQ ID NOs: 1-35 in US Patent Publication No. US20090226470, SEQ ID NOs: 1-35 in US Patent Publication US20130177581, SEQ ID NOs: 1-35 in International Patent Publication No. WO2009075886, SEQ ID NOs: 1-5, and 7-645 in International Patent Publication No. WO2012009644, SEQ ID NO: 1 in International Patent Publication No. WO1999024595, SEQ ID NO: 1 in US Patent No. US6310197, and SEQ ID NO: 1 in US Patent No. US6849405, each of which is herein incorporated by reference in its entirety.

**[00168]** In yet another non-limiting example, the TEE may be an internal ribosome entry site (IRES), HCV-IRES or an IRES element such as, but not limited to, those described in US Patent No. US7468275, US Patent Publication Nos. US20070048776 and US20110124100 and International Patent Publication Nos. WO2007025008 and WO2001055369, each of which is herein incorporated by reference in its entirety. The IRES elements may include, but are not limited to, the Gtx sequences (e.g., Gtx9-nt, Gtx8-nt, Gtx7-nt) described by Chappell et al. (Proc. Natl. Acad. Sci. USA 101:9590-9594, 2004) and Zhou et al. (PNAS 102:6273-6278, 2005) and in US Patent Publication Nos. US20070048776 and US20110124100 and International Patent Publication No. WO2007025008, each of which is herein incorporated by reference in its entirety.

**[00169]** "Translational enhancer polynucleotides" or "translation enhancer polynucleotide sequences" are polynucleotides which include one or more of the specific

TEE exemplified herein and/or disclosed in the art (see e.g., US6310197, US6849405, US7456273, US7183395, US20090226470, US20070048776, US20110124100, US20090093049, US20130177581, WO2009075886, WO2007025008, WO2012009644, WO2001055371 WO1999024595, and EP2610341A1 and EP2610340A1; each of which is herein incorporated by reference in its entirety) or their variants, homologs or functional derivatives. One or multiple copies of a specific TEE can be present in the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA. The TEEs in the translational enhancer polynucleotides can be organized in one or more sequence segments. A sequence segment can harbor one or more of the specific TEEs exemplified herein, with each TEE being present in one or more copies. When multiple sequence segments are present in a translational enhancer polynucleotide, they can be homogenous or heterogeneous. Thus, the multiple sequence segments in a translational enhancer polynucleotide can harbor identical or different types of the specific TEEs exemplified herein, identical or different number of copies of each of the specific TEEs, and/or identical or different organization of the TEEs within each sequence segment.

**[00170]** In one embodiment, the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA may include at least one TEE that is described in International Patent Publication No. WO1999024595, WO2012009644, WO2009075886, WO2007025008, WO1999024595, European Patent Publication No. EP2610341A1 and EP2610340A1, US Patent No. US6310197, US6849405, US7456273, US7183395, US Patent Publication No. US20090226470, US20110124100, US20070048776, US20090093049 and US20130177581, each of which is herein incorporated by reference in its entirety. The TEE may be located in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA.

**[00171]** In another embodiment, the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA may include at least one TEE that has at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identity with the TEEs described in US Patent Publication Nos. US20090226470, US20070048776, US20130177581 and US20110124100, International Patent Publication No. WO1999024595, WO2012009644,

WO2009075886 and WO2007025008, European Patent Publication No. EP2610341A1 and EP2610340A1, US Patent No. US6310197, US6849405, US7456273, US7183395, each of which is herein incorporated by reference in its entirety.

**[00172]** In one embodiment, the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA may include at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18 at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55 or more than 60 TEE sequences. The TEE sequences in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may be the same or different TEE sequences. The TEE sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times. In these patterns, each letter, A, B, or C represent a different TEE sequence at the nucleotide level.

**[00173]** In one embodiment, the 5'UTR may include a spacer to separate two TEE sequences. As a non-limiting example, the spacer may be a 15 nucleotide spacer and/or other spacers known in the art. As another non-limiting example, the 5'UTR may include a TEE sequence-spacer module repeated at least once, at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times and at least 9 times or more than 9 times in the 5'UTR.

**[00174]** In another embodiment, the spacer separating two TEE sequences may include other sequences known in the art which may regulate the translation of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention such as, but not limited to, miR sequences described herein (e.g., miR binding sites and miR seeds). As a non-limiting example, each spacer used to separate two TEE sequences may include a different miR sequence or component of a miR sequence (e.g., miR seed sequence).

**[00175]** In one embodiment, the TEE in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may include at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at

least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or more than 99% of the TEE sequences disclosed in US Patent Publication Nos. US20090226470, US20070048776, US20130177581 and US20110124100, International Patent Publication No. WO1999024595, WO2012009644, WO2009075886 and WO2007025008, European Patent Publication No. EP2610341A1 and EP2610340A1, US Patent No. US6310197, US6849405, US7456273, US7183395. In another embodiment, the TEE in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may include a 5-30 nucleotide fragment, a 5-25 nucleotide fragment, a 5-20 nucleotide fragment, a 5-15 nucleotide fragment, a 5-10 nucleotide fragment of the TEE sequences disclosed in US Patent Publication Nos. US20090226470, US20070048776, US20130177581 and US20110124100, International Patent Publication No. WO1999024595, WO2012009644, WO2009075886 and WO2007025008, European Patent Publication No. EP2610341A1 and EP2610340A1, US Patent No. US6310197, US6849405, US7456273, US7183395; each of which are herein incorporated by reference in their entirety.

**[00176]** In one embodiment, the TEE in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may include at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or more than 99% of the TEE sequences disclosed in Chappell et al. (Proc. Natl. Acad. Sci. USA 101:9590-9594, 2004) and Zhou et al. (PNAS 102:6273-6278, 2005), in Supplemental Table 1 and in Supplemental Table 2 disclosed by Wellensiek et al (Genome-wide profiling of human cap-independent translation-enhancing elements, Nature Methods, 2013; DOI:10.1038/NMETH.2522); each of which is herein incorporated by reference in its entirety. In another embodiment, the TEE in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may include a 5-30 nucleotide fragment, a 5-25 nucleotide fragment, a 5-20 nucleotide fragment, a 5-15 nucleotide fragment, a 5-10 nucleotide fragment of the TEE sequences disclosed in Chappell et al. (Proc. Natl. Acad.

Sci. USA 101:9590-9594, 2004) and Zhou et al. (PNAS 102:6273-6278, 2005), in Supplemental Table 1 and in Supplemental Table 2 disclosed by Wellensiek et al (Genome-wide profiling of human cap-independent translation-enhancing elements, Nature Methods, 2013; DOI:10.1038/NMETH.2522); each of which is herein incorporated by reference in its entirety.

**[00177]** In one embodiment, the TEE used in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention is an IRES sequence such as, but not limited to, those described in US Patent No. US7468275 and International Patent Publication No. WO2001055369, each of which is herein incorporated by reference in its entirety.

**[00178]** In one embodiment, the TEEs used in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may be identified by the methods described in US Patent Publication No. US20070048776 and US20110124100 and International Patent Publication Nos. WO2007025008 and WO2012009644, each of which is herein incorporated by reference in its entirety.

**[00179]** In another embodiment, the TEEs used in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may be a transcription regulatory element described in US Patent No. US7456273 and US7183395, US Patent Publication No. US20090093049, and International Publication No. WO2001055371, each of which is herein incorporated by reference in their entirety. The transcription regulatory elements may be identified by methods known in the art, such as, but not limited to, the methods described in US Patent No. US7456273 and US7183395, US Patent Publication No. US20090093049, and International Publication No. WO2001055371, each of which is herein incorporated by reference in their entirety.

**[00180]** In yet another embodiment, the TEE used in the 5'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention is an oligonucleotide or portion thereof as described in US Patent No. US7456273 and US7183395, US Patent Publication No. US20090093049, and

International Publication No. WO2001055371, each of which is herein incorporated by reference in their entirety.

**[00181]** The 5' UTR comprising at least one TEE described herein may be incorporated in a monocistronic sequence such as, but not limited to, a vector system or a nucleic acid vector. As a non-limiting example, the vector systems and nucleic acid vectors may include those described in US Patent Nos. 7456273 and US7183395, US Patent Publication No. US20070048776, US20090093049 and US20110124100 and International Patent Publication Nos. WO2007025008 and WO2001055371, each of which is herein incorporated by reference in its entirety.

**[00182]** In one embodiment, the TEEs described herein may be located in the 5'UTR and/or the 3'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA. The TEEs located in the 3'UTR may be the same and/or different than the TEEs located in and/or described for incorporation in the 5'UTR.

**[00183]** In one embodiment, the 3'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA may include at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18 at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55 or more than 60 TEE sequences. The TEE sequences in the 3'UTR of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention may be the same or different TEE sequences. The TEE sequences may be in a pattern such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than three times. In these patterns, each letter, A, B, or C represent a different TEE sequence at the nucleotide level.

**[00184]** In one embodiment, the 3'UTR may include a spacer to separate two TEE sequences. As a non-limiting example, the spacer may be a 15 nucleotide spacer and/or other spacers known in the art. As another non-limiting example, the 3'UTR may include a TEE sequence-spacer module repeated at least once, at least twice, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times and at least 9 times or more than 9 times in the 3'UTR.

**[00185]** In another embodiment, the spacer separating two TEE sequences may include other sequences known in the art which may regulate the translation of the signal-sensor polynucleotides, primary constructs, modified nucleic acids and/or mmRNA of the present invention such as, but not limited to, miR sequences described herein (e.g., miR binding sites and miR seeds). As a non-limiting example, each spacer used to separate two TEE sequences may include a different miR sequence or component of a miR sequence (e.g., miR seed sequence).

**[00186]** In one embodiment, the incorporation of a miR sequence and/or a TEE sequence changes the shape of the stem loop region which may increase and/or descrease translation. (see e.g, Kedde et al. A Pumilio-induced RNA structure switch in p27-3'UTR controls miR-221 and miR-22 accessibility. Nature Cell Biology. 2010, herein incorporated by reference in its entirety).

**[00187]** In one embodiment, the 5'UTR may comprise at least one microRNA sequence. The microRNA sequence may be, but is not limited to, a 19 or 22 nucleotide sequence and/or a microRNA sequence without the seed.

**[00188]** In one embodiment the microRNA sequence in the 5'UTR may be used to stabilize the nucleic acid and/or mRNA described herein.

**[00189]** In another embodiment, a microRNA sequence in the 5'UTR may be used to decrease the accessibility of the site of translation initiation such as, but not limited to a start codon. Matsuda et al (PLoS One. 2010 11(5):e15057; herein incorporated by reference in its entirety) used antisense locked nucleic acid (LNA) oligonucleotides and exon-junctino complexes (EJCs) around a start codon (-4 to +37 where the A of the AUG codons is +1) in order to decrease the accessibility to the first start codon (AUG). Matsuda showed that altering the sequence around the start codon with an LNA or EJC the efficiency, length and structural stability of the nucleic acid or mRNA is affected. The signal-sensor polynucleotides of the present invention may comprise a microRNA sequence, instead of the LNA or EJC sequence described by Matsuda et al, near the site of translation initiation in order to decrease the accessibility to the site of translation initiation. The site of translation initiation may be prior to, after or within the microRNA sequence. As a non-limiting example, the site of translation initiation may be located within a microRNA sequence such as a seed sequence or binding site. As another non-

limiting example, the site of translation initiation may be located within a miR-122 sequence such as the seed sequence or the mir-122 binding site.

**[00190]** In one embodiment, the nucleic acids or mRNA of the present invention comprises at least one microRNA sequence in a region of the nucleic acid or mRNA which may interact with a RNA binding protein.

*RNA Motifs for RNA Binding Proteins (RBPs)*

**[00191]** RNA binding proteins (RBPs) can regulate numerous aspects of co- and post-transcription gene expression such as, but not limited to, RNA splicing, localization, translation, turnover, polyadenylation, capping, modification, export and localization. RNA-binding domains (RBDs), such as, but not limited to, RNA recognition motif (RR) and hnRNP K-homology (KH) domains, typically regulate the sequence association between RBPs and their RNA targets (Ray et al. Nature 2013. 499:172-177; herein incorporated by reference in its entirety). In one embodiment, the canonical RBDs can bind short RNA sequences. In another embodiment, the canonical RBDs can recognize structure RNAs.

**[00192]** In one embodiment, the nucleic acids and/or mRNA may comprise at least one RNA-binding motif such as, but not limited to a RNA-binding domain (RBD).

**[00193]** In one embodiment, the RBD may be any of the RBDs, fragments or variants thereof descried by Ray et al. (Nature 2013. 499:172-177; herein incorporated by reference in its entirety).

**[00194]** In one embodiment, the nucleic acids or mRNA of the present invention may comprise a sequence for at least one RNA-binding domain (RBDs). When the nucleic acids or mRNA of the present invention comprise more than one RBD, the RBDs do not need to be from the same species or even the same structural class.

**[00195]** In one embodiment, at least one flanking region (e.g., the 5'UTR and/or the 3'UTR) may comprise at least one RBD. In another embodiment, the first flanking region and the second flanking region may both comprise at least one RBD. The RBD may be the same or each of the RBDs may have at least 60% sequence identity to the other RBD. As a non-limiting example, at least on RBD may be located before, after and/or within the 3'UTR of the nucleic acid or mRNA of the present invention. As

another non-limiting example, at least one RBD may be located before or within the first 300 nucleosides of the 3'UTR.

**[00196]** In another embodiment, the nucleic acids and/or mRNA of the present invention may comprise at least one RBD in the first region of linked nucleosides. The RBD may be located before, after or within a coding region (e.g., the ORF).

**[00197]** In yet another embodiment, the first region of linked nucleosides and/or at least one flanking region may comprise at least on RBD. As a non-limiting example, the first region of linked nucleosides may comprise a RBD related to splicing factors and at least one flanking region may comprise a RBD for stability and/or translation factors.

**[00198]** In one embodiment, the nucleic acids and/or mRNA of the present invention may comprise at least one RBD located in a coding and/or non-coding region of the nucleic acids and/or mRNA.

**[00199]** In one embodiment, at least one RBD may be incorporated into at least one flanking region to increase the stability of the nucleic acid and/or mRNA of the present invention.

**[00200]** In one embodiment, a microRNA sequence in a RNA binding protein motif may be used to decrease the accessibility of the site of translation initiation such as, but not limited to a start codon. The signal-sensor polynucleotdies of the present invention may comprise a microRNA sequence, instead of the LNA or EJC sequence described by Matsuda et al, near the site of translation initiation in order to decrease the accessibility to the site of translation initiation. The site of translation initiation may be prior to, after or within the microRNA sequence. As a non-limiting example, the site of translation initiation may be located within a microRNA sequence such as a seed sequence or binding site. As another non-limiting example, the site of translation initiation may be located within a miR-122 sequence such as the seed sequence or the mir-122 binding site.

**[00201]** In another embodiment, an antisense locked nucleic acid (LNA) oligonucleotides and exon-junctino complexes (EJCs) may be used in the RNA binding protein motif. The LNA and EJCs may be used around a start codon (-4 to +37 where the A of the AUG codons is +1) in order to decrease the accessibility to the first start codon (AUG).

*3' UTR and the AU Rich Elements*

**[00202]** 3′UTRs are known to have stretches of Adenosines and Uridines embedded in them. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995): Class I AREs contain several dispersed copies of an AUUUA motif within U-rich regions. C-Myc and MyoD contain class I AREs. Class II AREs possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Molecules containing this type of AREs include GM-CSF and TNF-a. Class III ARES are less well defined. These U rich regions do not contain an AUUUA motif. c-Jun and Myogenin are two well-studied examples of this class. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

**[00203]** Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of signal-sensor polynucleotides, primary constructs or mmRNA of the invention. When engineering specific polynucleotides, primary constructs or mmRNA, one or more copies of an ARE can be introduced to make polynucleotides, primary constructs or mmRNA of the invention less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein. Transfection experiments can be conducted in relevant cell lines, using signal-sensor polynucleotides, primary constructs or mmRNA of the invention and protein production can be assayed at various time points post-transfection. For example, cells can be transfected with different ARE-engineering molecules and by using an ELISA kit to the relevant protein and assaying protein produced at 6 hr, 12 hr, 24 hr, 48 hr, and 7 days post-transfection.

*3' UTR and Triple Helices*

**[00204]** In one embodiment, signal-sequence polynucleotides of the present invention may include a triple helix on the 3' end of the signal-sequence polynucleotides. The 3'

end of the nucleic acids of the present invention may include a triple helix alone or in combination with a Poly-A tail.

**[00205]** In one embodiment, the signal-sequence polynucleotides of the present invention may comprise at least a first and a second U-rich region, a conserved stem loop region between the first and second region and an A-rich region. The first and second U-rich region and the A-rich region may associate to form a triple helix on the 3' end of the nucleic acid. This triple helix may stabilize the nucleic acid, enhance the translational efficiency of the nucleic acid and/or protect the 3' end from degradation. Exemplary triple helices include, but are not limited to, the triple helix sequence of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), MEN-β and polyadenylated nuclear (PAN) RNA (See Wilusz et al., Genes & Development 2012 26:2392-2407; herein incorporated by reference in its entirety). In one embodiment, the 3' end of the modified nucleic acids, enhanced modified RNA or ribonucleic acids of the present invention comprises a first U-rich region comprising TTTTTCTTTT (SEQ ID NO: 1), a second U-rich region comprising TTTTGCTTTTT (SEQ ID NO: 2) or TTTTGCTTTT (SEQ ID NO: 3), an A-rich region comprising AAAAAGCAAAA (SEQ ID NO: 4). In another embodiment, the 3' end of the nucleic acids of the present invention comprises a triple helix formation structure comprising a first U-rich region, a conserved region, a second U-rich region and an A-rich region.

**[00206]** In one embodiment, the triple helix may be formed from the cleavage of a MALAT1 sequence prior to the cloverleaf structure. While not meaning to be bound by theory, MALAT1 is a long non-coding RNA which, when cleaved, forms a triple helix and a tRNA-like cloverleaf structure. The MALAT1 transcript then localizes to nuclear speckles and the tRNA-like cloverleaf localizes to the cytoplasm (Wilusz et al. Cell 2008 135(5): 919-932; herein incorporated by reference in its entirety).

**[00207]** As a non-limiting example, the terminal end of the nucleic acid of the present invention comprising the MALAT1 sequence can then form a triple helix structure, after RNaseP cleavage from the cloverleaf structure, which stabilizes the nucleic acid (Peart et al. *Non-mRNA 3' end formation: how the other half lives*; WIREs RNA 2013; herein incorporated by reference in its entirety).

**[00208]** In one embodiment, the signal-sequence polynucleotides described herein comprise a MALAT1 sequence. In another embodiment, the signal-sequence polynucleotides may be polyadenylated. In yet another embodiment, the signal-sequence polynucleotides is not polyadenylated but has an increased resistance to degradation compared to unmodified nucleic acids or mRNA.

**[00209]** In one embodiment, the signal-sequence polynucleotides of the present invention may comprise a MALAT1 sequence in the second flanking region (e.g., the 3'UTR). As a non-limiting example, the MALAT1 sequence may be human or mouse.

**[00210]** In another embodiment, the cloverleaf structure of the MALAT1 sequence may also undergo processing by RNaseZ and CCA adding enzyme to form a tRNA-like structure called mascRNA (MALAT1-associated small cytoplasmic RNA). As a non-limiting example, the mascRNA may encode a protein or a fragment thereof and/or may comprise a microRNA sequence. The mascRNA may comprise at least one chemical modification described herein.

*Stem Loop*

**[00211]** In one embodiment, the nucleic acids of the present invention may include a stem loop such as, but not limited to, a histone stem loop. The stem loop may be a nucleotide sequence that is about 25 or about 26 nucleotides in length such as, but not limited to, SEQ ID NOs: 7-17 as described in International Patent Publication No. WO2013103659, herein incorporated by reference in its entirety. The histone stem loop may be located 3' relative to the coding region (e.g., at the 3' terminus of the coding region). As a non-limiting example, the stem loop may be located at the 3' end of a nucleic acid described herein.

**[00212]** In one embodiment, the stem loop may be located in the second terminal region. As a non-limiting example, the stem loop may be located within an untranslated region (e.g., 3'UTR) in the second terminal region.

**[00213]** In one embodiment, the nucleic acid such as, but not limited to mRNA, which comprises the histone stem loop may be stabilized by the addition of at least one chain terminating nucleoside. Not wishing to be bound by theory, the addition of at least one chain terminating nucleoside may slow the degradation of a nucleic acid and thus can increase the half-life of the nucleic acid.

**[00214]** In one embodiment, the chain terminating nucleoside may be, but is not limited to, those described in International Patent Publication No. WO2013103659, herein incorporated by reference in its entirety. In another embodiment, the chain terminating nucleosides which may be used with the present invention includes, but is not limited to, 3'-deoxyadenosine (cordycepin), 3'-deoxyuridine, 3'-deoxycytosine, 3'-deoxyguanosine, 3'-deoxythymine, 2',3'-dideoxynucleosides, such as 2',3'-dideoxyadenosine, 2',3'-dideoxyuridine, 2',3'-dideoxycytosine, 2',3'- dideoxyguanosine, 2',3'-dideoxythymine, a 2'-deoxynucleoside, or a -O- methylnucleoside.

**[00215]** In another embodiment, the nucleic acid such as, but not limited to mRNA, which comprises the histone stem loop may be stabilized by a modification to the 3'region of the nucleic acid that can prevent and/or inhibit the addition of oligio(U) (see e.g., International Patent Publication No. WO2013103659, herein incorporated by reference in its entirety).

**[00216]** In yet another embodiment, the nucleic acid such as, but not limited to mRNA, which comprises the histone stem loop may be stabilized by the addition of an oligonucleotide that terminates in a 3'-deoxynucleoside, 2',3'-dideoxynucleoside 3'-0-methylnucleosides, 3'-0-ethylnucleosides, 3'-arabinosides, and other modified nucleosides known in the art and/or described herein.

**[00217]** In one embodiment, the nucleic acids of the present invention may include a histone stem loop, a polyA tail sequence and/or a 5'cap structure. The histone stem loop may be before and/or after the polyA tail sequence. The nucleic acids comprising the histone stem loop and a polyA tail sequence may include a chain terminating nucleoside described herein.

**[00218]** In another embodiment, the nucleic acids of the present invention may include a histone stem loop and a 5'cap structure. The 5'cap structure may include, but is not limited to, those described herein and/or known in the art.

**[00219]** In one embodiment, the conserved stem loop region may comprise a miR sequence described herein. As a non-limiting example, the stem loop region may comprise the seed sequence of a miR sequence described herein. In another non-limiting example, the stem loop region may comprise a miR-122 seed sequence.

**[00220]** In another embodiment, the conserved stem loop region may comprise a miR sequence described herein and may also include a TEE sequence.

**[00221]** In one embodiment, the incorporation of a miR sequence and/or a TEE sequence changes the shape of the stem loop region which may increase and/or descrease translation. (see e.g, Kedde et al. A Pumilio-induced RNA structure switch in p27-3'UTR controls miR-221 and miR-22 accessibility. Nature Cell Biology. 2010, herein incorporated by reference in its entirety).

*5′ Capping*

**[00222]** The 5′ cap structure of an mRNA is involved in nuclear export, increasing mRNA stability and binds the mRNA Cap Binding Protein (CBP), which is responsibile for mRNA stability in the cell and translation competency through the association of CBP with poly(A) binding protein to form the mature cyclic mRNA species. The cap further assists the removal of 5′ proximal introns removal during mRNA splicing.

**[00223]** Endogenous mRNA molecules may be 5′-end capped generating a 5′-ppp-5′-triphosphate linkage between a terminal guanosine cap residue and the 5′-terminal transcribed sense nucleotide of the mRNA molecule. This 5′-guanylate cap may then be methylated to generate an N7-methyl-guanylate residue. The ribose sugars of the terminal and/or anteterminal transcribed nucleotides of the 5′ end of the mRNA may optionally also be 2′-O-methylated. 5′-decapping through hydrolysis and cleavage of the guanylate cap structure may target a nucleic acid molecule, such as an mRNA molecule, for degradation.

**[00224]** Modifications to the signal-sensor polynucleotides, primary constructs, and mmRNA of the present invention may generate a non-hydrolyzable cap structure preventing decapping and thus increasing mRNA half-life. Because cap structure hydrolysis requires cleavage of 5′-ppp-5′ phosphorodiester linkages, modified nucleotides may be used during the capping reaction. For example, a Vaccinia Capping Enzyme from New England Biolabs (Ipswich, MA) may be used with α-thio-guanosine nucleotides according to the manufacturer's instructions to create a phosphorothioate linkage in the 5′-ppp-5′ cap. Additional modified guanosine nucleotides may be used such as α-methyl-phosphonate and seleno-phosphate nucleotides.

**[00225]** Additional modifications include, but are not limited to, 2′-O-methylation of the ribose sugars of 5′-terminal and/or 5′-anteterminal nucleotides of the mRNA (as mentioned above) on the 2′-hydroxyl group of the sugar ring. Multiple distinct 5′-cap structures can be used to generate the 5′-cap of a nucleic acid molecule, such as an mRNA molecule.

**[00226]** Cap analogs, which herein are also referred to as synthetic cap analogs, chemical caps, chemical cap analogs, or structural or functional cap analogs, differ from natural (i.e. endogenous, wild-type or physiological) 5′-caps in their chemical structure, while retaining cap function. Cap analogs may be chemically (i.e. non-enzymatically) or enzymatically synthesized and/linked to a nucleic acid molecule.

**[00227]** For example, the Anti-Reverse Cap Analog (ARCA) cap contains two guanines linked by a 5′-5′-triphosphate group, wherein one guanine contains an N7 methyl group as well as a 3′-O-methyl group (i.e., N7,3′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine ($m^7$G-3′mppp-G; which may equivaliently be designated 3′ O-Me-m7G(5')ppp(5')G). The 3′-O atom of the other, unmodified, guanine becomes linked to the 5′-terminal nucleotide of the capped nucleic acid molecule (e.g. an mRNA or mmRNA). The N7- and 3′-O-methlyated guanine provides the terminal moiety of the capped nucleic acid molecule (e.g. mRNA or mmRNA).

**[00228]** Another exemplary cap is mCAP, which is similar to ARCA but has a 2′-O-methyl group on guanosine (i.e., N7,2′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine, $m^7$Gm-ppp-G).

**[00229]** While cap analogs allow for the concomitant capping of a nucleic acid molecule in an in vitro transcription reaction, up to 20% of transcripts remain uncapped. This, as well as the structural differences of a cap analog from an endogenous 5′-cap structures of nucleic acids produced by the endogenous, cellular transcription machinery, may lead to reduced translational competency and reduced cellular stability.

**[00230]** Signal-sensor polynucleotides, primary constructs and mmRNA of the invention may also be capped post-transcriptionally, using enzymes, in order to generate more authentic 5′-cap structures. As used herein, the phrase "more authentic" refers to a feature that closely mirrors or mimics, either structurally or functionally, an endogenous or wild type feature. That is, a "more authentic" feature is better representative of an

endogenous, wild-type, natural or physiological cellular function and/or structure as compared to synthetic features or analogs, etc., of the prior art, or which outperforms the corresponding endogenous, wild-type, natural or physiological feature in one or more respects. Non-limiting examples of more authentic 5′cap structures of the present invention are those which, among other things, have enhanced binding of cap binding proteins, increased half life, reduced susceptibility to 5′ endonucleases and/or reduced 5′decapping, as compared to synthetic 5′cap structures known in the art (or to a wild-type, natural or physiological 5′cap structure). For example, recombinant Vaccinia Virus Capping Enzyme and recombinant 2′-O-methyltransferase enzyme can create a canonical 5′-5′-triphosphate linkage between the 5′-terminal nucleotide of an mRNA and a guanine cap nucleotide wherein the cap guanine contains an N7 methylation and the 5′-terminal nucleotide of the mRNA contains a 2′-O-methyl. Such a structure is termed the Cap1 structure. This cap results in a higher translational-competency and cellular stability and a reduced activation of cellular pro-inflammatory cytokines, as compared, e.g., to other 5′cap analog structures known in the art. Cap structures include 7mG(5')ppp(5')N,pN2p (cap 0), 7mG(5')ppp(5')NlmpNp (cap 1), and 7mG(5')-ppp(5')NlmpN2mp (cap 2).

**[00231]** Because the signal-sensor polynucleotides, primary constructs or mmRNA may be capped post-transcriptionally, and because this process is more efficient, nearly 100% of the signal-sensor polynucleotides, primary constructs or mmRNA may be capped. This is in contrast to ~80% when a cap analog is linked to an mRNA in the course of an *in vitro* transcription reaction.

**[00232]** According to the present invention, 5′ terminal caps may include endogenous caps or cap analogs. According to the present invention, a 5′ terminal cap may comprise a guanine analog. Useful guanine analogs include inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

*Viral Sequences*

**[00233]** Additional viral sequences such as, but not limited to, the translation enhancer sequence of the barley yellow dwarf virus (BYDV-PAV) can be engineered and inserted in the 3′ UTR of the signal-sensor polynucleotides, primary constructs or mmRNA of the invention and can stimulate the translation of the construct *in vitro* and *in vivo*.

Transfection experiments can be conducted in relevant cell lines at and protein production can be assayed by ELISA at 12hr, 24hr, 48hr, 72 hr and day 7 post-transfection.

*IRES Sequences*

**[00234]** Further, provided are signal-sensor polynucleotides, primary constructs or mmRNA which may contain an internal ribosome entry site (IRES). First identified as a feature Picorna virus RNA, IRES plays an important role in initiating protein synthesis in absence of the 5′ cap structure. An IRES may act as the sole ribosome binding site, or may serve as one of multiple ribosome binding sites of an mRNA. signal-sensor polynucleotides, primary constructs or mmRNA containing more than one functional ribosome binding site may encode several oncology-related peptides or oncology-related polypeptides that are translated independently by the ribosomes ("multicistronic nucleic acid molecules"). When signal-sensor polynucleotides, primary constructs or mmRNA are provided with an IRES, further optionally provided is a second translatable region. Examples of IRES sequences that can be used according to the invention include without limitation, those from picornaviruses (e.g. FMDV), pest viruses (CFFV), polio viruses (PV), encephalomyocarditis viruses (ECMV), foot-and-mouth disease viruses (FMDV), hepatitis C viruses (HCV), classical swine fever viruses (CSFV), murine leukemia virus (MLV), simian immune deficiency viruses (SIV) or cricket paralysis viruses (CrPV).

*Poly-A tails*

**[00235]** During RNA processing, a long chain of adenine nucleotides (poly-A tail) may be added to a polynucleotide such as an mRNA molecule in order to increase stability. Immediately after transcription, the 3' end of the transcript may be cleaved to free a 3' hydroxyl. Then poly-A polymerase adds a chain of adenine nucleotides to the RNA. The process, called polyadenylation, adds a poly-A tail that can be between 100 and 250 residues long.

**[00236]** It has been discovered that unique poly-A tail lengths provide certain advantages to the signal-sensor polynucleotides, primary constructs or mmRNA of the present invention.

**[00237]** Generally, the length of a poly-A tail of the present invention is greater than 30 nucleotides in length. In another embodiment, the poly-A tail is greater than 35

nucleotides in length (e.g., at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000 nucleotides). In some embodiments, the signal-sensor polynucleotides, primary construct, or mmRNA includes from about 30 to about 3,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 750, from 30 to 1,000, from 30 to 1,500, from 30 to 2,000, from 30 to 2,500, from 50 to 100, from 50 to 250, from 50 to 500, from 50 to 750, from 50 to 1,000, from 50 to 1,500, from 50 to 2,000, from 50 to 2,500, from 50 to 3,000, from 100 to 500, from 100 to 750, from 100 to 1,000, from 100 to 1,500, from 100 to 2,000, from 100 to 2,500, from 100 to 3,000, from 500 to 750, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 2,500, from 500 to 3,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 2,500, from 1,000 to 3,000, from 1,500 to 2,000, from 1,500 to 2,500, from 1,500 to 3,000, from 2,000 to 3,000, from 2,000 to 2,500, and from 2,500 to 3,000).

**[00238]** In one embodiment, the poly-A tail is designed relative to the length of the overall signal-sensor polynucleotides, primary constructs or mmRNA. This design may be based on the length of the coding region, the length of a particular feature or region (such as the first or flanking regions), or based on the length of the ultimate product expressed from the polynucleotides, primary constructs or mmRNA.

**[00239]** In this context the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100% greater in length than the signal-sensor polynucleotides, primary constructs or mmRNA or feature thereof. The poly-A tail may also be designed as a fraction of polynucleotides, primary constructs or mmRNA to which it belongs. In this context, the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, or 90% or more of the total length of the construct or the total length of the construct minus the poly-A tail.

**[00240]** In one embodiment, engineered binding sites and/or conjugation of signal-sensor polynucleotides, primary constructs or mmRNA for Poly-A binding protein may be used to enhance expression. The engineered binding sites may be sensor sequences which can operate as binding sites for ligands of the local microenvironment of the nucleic acids and/or mRNA. As a non-limiting example, the nucleic acids and/or mRNA may comprise at least one engineered binding site to alter the binding affinity of Poly-A

binding protein (PABP) and analogs thereof. The incorporation of at least one engineered binding site may increase the binding affinity of the PABP and analogs thereof.

**[00241]** Additionally, multiple distinct signal-sensor polynucleotides, primary constructs or mmRNA may be linked together to the PABP (Poly-A binding protein) through the 3′-end using modified nucleotides at the 3′-terminus of the poly-A tail. Transfection experiments can be conducted in relevant cell lines and protein production can be assayed by ELISA at 12hr, 24hr, 48hr, 72 hr and day 7 post-transfection. As a non-limiting example, the transfection experiments may be used to evaluate the effect on PABP or analogs thereof binding affinity as a result of the addition of at least one engineered binding site.

**[00242]** In one embodiment, the signal-sensor polynucleotides and primary constructs of the present invention are designed to include a polyA-G Quartet. The G-quartet is a cyclic hydrogen bonded array of four guanine nucleotides that can be formed by G-rich sequences in both DNA and RNA. In this embodiment, the G-quartet is incorporated at the end of the poly-A tail. The resultant mmRNA construct is assayed for stability, protein production and other parameters including half-life at various time points. It has been discovered that the polyA-G quartet results in protein production equivalent to at least 75% of that seen using a poly-A tail of 120 nucleotides alone.

**[00243]** In one embodiment, the nucleic acids or mRNA of the present invention may comprise a polyA tail and may be stabilized by the addition of a chain terminating nucleoside. The nucleic acids and/or mRNA with a polyA tail may further comprise a 5'cap structure.

**[00244]** In another embodiment, the nucleic acids or mRNA of the present invention may comprise a polyA-G Quartet. The nucleic acids and/or mRNA with a polyA-G Quartet may further comprise a 5'cap structure.

**[00245]** In one embodiment, the chain terminating nucleoside which may be used to stabilize the nucleic acid or mRNA comprising a polyA tail or polyA-G Quartet may be, but is not limited to, those described in International Patent Publication No. WO2013103659, herein incorporated by reference in its entirety. In another embodiment, the chain terminating nucleosides which may be used with the present

invention includes, but is not limited to, 3'-deoxyadenosine (cordycepin), 3'-deoxyuridine, 3'-deoxycytosine, 3'-deoxyguanosine, 3'-deoxythymine, 2',3'-dideoxynucleosides, such as 2',3'- dideoxyadenosine, 2',3'-dideoxyuridine, 2',3'-dideoxycytosine, 2',3'- dideoxyguanosine, 2',3'-dideoxythymine, a 2'-deoxynucleoside, or a -O- methylnucleoside.

**[00246]** In another embodiment, the nucleic acid such as, but not limited to mRNA, which comprise a polyA tail or a polyA-G Quartet may be stabilized by a modification to the 3'region of the nucleic acid that can prevent and/or inhibit the addition of oligio(U) (see e.g., International Patent Publication No. WO2013103659, herein incorporated by reference in its entirety).

**[00247]** In yet another embodiment, the nucleic acid such as, but not limited to mRNA, which comprise a polyA tail or a polyA-G Quartet may be stabilized by the addition of an oligonucleotide that terminates in a 3'-deoxynucleoside, 2',3'-dideoxynucleoside 3'-0- methylnucleosides, 3'-0-ethylnucleosides, 3'-arabinosides, and other modified nucleosides known in the art and/or described herein.

Quantification

**[00248]** In one embodiment, the signal-sensor polynucleotides, primary constructs or mmRNA of the present invention may be quantified in exosomes derived from one or more bodily fluid. As used herein "bodily fluids" include peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates, blastocyl cavity fluid, and umbilical cord blood. Alternatively, exosomes may be retrieved from an organ selected from the group consisting of lung, heart, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colon, breast, prostate, brain, esophagus, liver, and placenta.

**[00249]** In the quantification method, a sample of not more than 2mL is obtained from the subject and the exosomes isolated by size exclusion chromatography, density gradient

centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof. In the analysis, the level or concentration of signal-sensor polynucleotides, primary construct or mmRNA may be an expression level, presence, absence, truncation or alteration of the administered construct. It is advantageous to correlate the level with one or more clinical phenotypes or with an assay for a human disease biomarker. The assay may be performed using construct specific probes, cytometry, qRT-PCR, real-time PCR, PCR, flow cytometry, electrophoresis, mass spectrometry, or combinations thereof while the exosomes may be isolated using immunohistochemical methods such as enzyme linked immunosorbent assay (ELISA) methods. Exosomes may also be isolated by size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof.

**[00250]** These methods afford the investigator the ability to monitor, in real time, the level of signal-sensor polynucleotides, primary constructs or mmRNA remaining or delivered. This is possible because the polynucleotides, primary constructs or mmRNA of the present invention differ from the endogenous forms due to the structural and/or chemical modifications.

## II. Design and synthesis of signal-sensor polynucleotides

**[00251]** Signal-sensor polynucleotides, primary constructs or mmRNA for use in accordance with the invention may be prepared according to any available technique including, but not limited to chemical synthesis, enzymatic synthesis, which is generally termed *in vitro* transcription (IVT) or enzymatic or chemical cleavage of a longer precursor, etc. Methods of synthesizing RNAs are known in the art (see, *e.g.*, Gait, M.J. (ed.) *Oligonucleotide synthesis: a practical approach*, Oxford [Oxfordshire], Washington, DC: IRL Press, 1984; and Herdewijn, P. (ed.) *Oligonucleotide synthesis: methods and applications*, Methods in Molecular Biology, v. 288 (Clifton, N.J.) Totowa, N.J.: Humana Press, 2005; both of which are incorporated herein by reference).

**[00252]** The process of design and synthesis of the signal-sensor primary constructs of the invention generally includes the steps of gene construction, mRNA production (either with or without modifications) and purification. In the enzymatic synthesis method, a

target signal-sensor polynucleotide sequence encoding the oncology-related polypeptide of interest is first selected for incorporation into a vector which will be amplified to produce a cDNA template. Optionally, the target signal-sensor polynucleotide sequence and/or any flanking sequences may be codon optimized. The cDNA template is then used to produce mRNA through *in vitro* transcription (IVT). After production, the mRNA may undergo purification and clean-up processes. The steps of which are provided in more detail below.

*Gene Construction*

**[00253]** The step of gene construction may include, but is not limited to gene synthesis, vector amplification, plasmid purification, plasmid linearization and clean-up, and cDNA template synthesis and clean-up.

*Gene Synthesis*

**[00254]** Once an oncology-related polypeptide of interest, or target, is selected for production, a signal-sensor primary construct is designed. Within the primary construct, a first region of linked nucleosides encoding the polypeptide of interest may be constructed using an open reading frame (ORF) of a selected nucleic acid (DNA or RNA) transcript. The ORF may comprise the wild type ORF, an isoform, variant or a fragment thereof. As used herein, an "open reading frame" or "ORF" is meant to refer to a nucleic acid sequence (DNA or RNA) which is capable of encoding an oncology-related polypeptide of interest. ORFs often begin with the start codon, ATG and end with a nonsense or termination codon or signal.

**[00255]** Further, the nucleotide sequence of the first region may be codon optimized. Codon optimization methods are known in the art and may be useful in efforts to achieve one or more of several goals. These goals include to match codon frequencies in target and host organisms to ensure proper folding, bias GC content to increase mRNA stability or reduce secondary structures, minimize tandem repeat codons or base runs that may impair gene construction or expression, customize transcriptional and translational control regions, insert or remove protein trafficking sequences, remove/add post translation modification sites in encoded protein (e.g. glycosylation sites), add, remove or shuffle protein domains, insert or delete restriction sites, modify ribosome binding sites and mRNA degradation sites, to adjust translational rates to allow the various domains of

the protein to fold properly, or to reduce or eliminate problem secondary structures within the mRNA. Codon optimization tools, algorithms and services are known in the art, non-limiting examples include services from GeneArt (Life Technologies) and/or DNA2.0 (Menlo Park CA). In one embodiment, the ORF sequence is optimized using optimization algorithms. Codon options for each amino acid are given in Table 1.

**Table 1. Codon Options**

| Amino Acid | Single Letter Code | Codon Options |
|---|---|---|
| Isoleucine | I | ATT, ATC, ATA |
| Leucine | L | CTT, CTC, CTA, CTG, TTA, TTG |
| Valine | V | GTT, GTC, GTA, GTG |
| Phenylalanine | F | TTT, TTC |
| Methionine | M | ATG |
| Cysteine | C | TGT, TGC |
| Alanine | A | GCT, GCC, GCA, GCG |
| Glycine | G | GGT, GGC, GGA, GGG |
| Proline | P | CCT, CCC, CCA, CCG |
| Threonine | T | ACT, ACC, ACA, ACG |
| Serine | S | TCT, TCC, TCA, TCG, AGT, AGC |
| Tyrosine | Y | TAT, TAC |
| Tryptophan | W | TGG |
| Glutamine | Q | CAA, CAG |
| Asparagine | N | AAT, AAC |
| Histidine | H | CAT, CAC |
| Glutamic acid | E | GAA, GAG |
| Aspartic acid | D | GAT, GAC |
| Lysine | K | AAA, AAG |
| Arginine | R | CGT, CGC, CGA, CGG, AGA, AGG |
| Selenocysteine | Sec | UGA in mRNA in presence of Selenocystein insertion element (SECIS) |
| Stop codons | Stop | TAA, TAG, TGA |

**[00256]** In one embodiment, after a nucleotide sequence has been codon optimized it may be further evaluated for regions containing restriction sites. At least one nucleotide within the restriction site regions may be replaced with another nucleotide in order to remove the restriction site from the sequence but the replacement of nucleotides does alter the amino acid sequence which is encoded by the codon optimized nucleotide sequence.

**[00257]** Features, which may be considered beneficial in some embodiments of the present invention, may be encoded by the signal-sensor primary construct and may flank the ORF as a first or second flanking region. The flanking regions may be incorporated

into the signal-sensor primary construct before and/or after optimization of the ORF. It is not required that a signal-sensor primary construct contain both a 5′ and 3′ flanking region. Examples of such features include, but are not limited to, untranslated regions (UTRs), Kozak sequences, an oligo(dT) sequence, and detectable tags and may include multiple cloning sites which may have XbaI recognition.

**[00258]** In some embodiments, a 5′ UTR and/or a 3′ UTR may be provided as flanking regions. Multiple 5′ or 3′ UTRs may be included in the flanking regions and may be the same or of different sequences. Any portion of the flanking regions, including none, may be codon optimized and any may independently contain one or more different structural or chemical modifications, before and/or after codon optimization. Combinations of features may be included in the first and second flanking regions and may be contained within other features. For example, the ORF may be flanked by a 5' UTR which may contain a strong Kozak translational initiation signal and/or a 3' UTR which may include an oligo(dT) sequence for templated addition of a poly-A tail.

**[00259]** Tables 2 and 3 provide a listing of exemplary UTRs which may be utilized in the signal-sensor primary construct of the present invention as flanking regions. Shown in Table 2 is a representative listing of a 5′-untranslated region of the invention. Variants of 5’ UTRs may be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

**Table 2. 5′-Untranslated Regions**

| 5′ UTR Identifier | Name/ Description | Sequence | SEQ ID NO. |
|---|---|---|---|
| Native | Wild type UTR | See wild type sequence | - |
| 5UTR-001 | Synthetic UTR | GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCACC | 1 |
| 5UTR-002 | Upstream UTR | GGGAGATCAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCACC | 2 |
| 5UTR-003 | Upstream UTR | GGAATAAAAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCATTTCTTTTAAAGCAAAAGCAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCAAC | 3 |
| 5UTR-004 | Upstream UTR | GGGAGACAAGCUUGGCAUUCCGGUACUGUUGGUAAAGCCACC | 4 |

**[00260]** Shown in Table 3 is a representative listing of 3′-untranslated regions of the invention. Variants of 3' UTRs may be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

**Table 3. 3′-Untranslated Regions**

| 3′ UTR Identifier | Name/ Description | Sequence | SEQ ID NO. |
|---|---|---|---|
| 3UTR-001 | Creatine Kinase | GCGCCTGCCCACCTGCCACCGACTGCTGGAACC CAGCCAGTGGGAGGGCCTGGCCCACCAGAGTCC TGCTCCCTCACTCCTCGCCCCGCCCCCTGTCCCA GAGTCCCACCTGGGGGCTCTCTCCACCCTTCTCA GAGTTCCAGTTTCAACCAGAGTTCCAACCAATG GGCTCCATCCTCTGGATTCTGGCCAATGAAATAT CTCCCTGGCAGGGTCCTCTTCTTTTCCCAGAGCT CCACCCCAACCAGGAGCTCTAGTTAATGGAGAG CTCCCAGCACACTCGGAGCTTGTGCTTTGTCTCC ACGCAAAGCGATAAATAAAAGCATTGGTGGCCT TTGGTCTTTGAATAAAGCCTGAGTAGGAAGTCTA GA | 5 |
| 3UTR-002 | Myoglobin | GCCCCTGCCGCTCCCACCCCCACCCATCTGGGCC CCGGGTTCAAGAGAGAGCGGGGTCTGATCTCGT GTAGCCATATAGAGTTTGCTTCTGAGTGTCTGCT TTGTTTAGTAGAGGTGGGCAGGAGGAGCTGAGG GGCTGGGGCTGGGGTGTTGAAGTTGGCTTTGCAT GCCCAGCGATGCGCCTCCCTGTGGGATGTCATCA CCCTGGGAACCGGGAGTGGCCCTTGGCTCACTG TGTTCTGCATGGTTTGGATCTGAATTAATTGTCC TTTCTTCTAAATCCCAACCGAACTTCTTCCAACC TCCAAACTGGCTGTAACCCCAAATCCAAGCCATT AACTACACCTGACAGTAGCAATTGTCTGATTAAT CACTGGCCCCTTGAAGACAGCAGAATGTCCCTTT GCAATGAGGAGGAGATCTGGGCTGGGCGGGCCA GCTGGGGAAGCATTTGACTATCTGGAACTTGTGT GTGCCTCCTCAGGTATGGCAGTGACTCACCTGGT TTTAATAAAACAACCTGCAACATCTCATGGTCTT TGAATAAAGCCTGAGTAGGAAGTCTAGA | 6 |
| 3UTR-003 | α-actin | ACACACTCCACCTCCAGCACGCGACTTCTCAGG ACGACGAATCTTCTCAATGGGGGGGCGGCTGAG CTCCAGCCACCCCGCAGTCACTTTCTTTGTAACA ACTTCCGTTGCTGCCATCGTAAACTGACACAGTG TTTATAACGTGTACATACATTAACTTATTACCTC ATTTTGTTATTTTTCGAAACAAAGCCCTGTGGAA GAAAATGGAAAACTTGAAGAAGCATTAAAGTCA TTCTGTTAAGCTGCGTAAATGGTCTTTGAATAAA GCCTGAGTAGGAAGTCTAGA | 7 |
| 3UTR-004 | Albumin | CATCACATTTAAAAGCATCTCAGCCTACCATGAG AATAAGAGAAAGAAAATGAAGATCAAAAGCTT ATTCATCTGTTTTTCTTTTTCGTTGGTGTAAAGCC | 8 |

| | | | |
|---|---|---|---|
| | | AACACCCTGTCTAAAAAACATAAATTTCTTTAAT CATTTTGCCTCTTTTCTCTGTGCTTCAATTAATAA AAAATGGAAAGAATCTAATAGAGTGGTACAGCA CTGTTATTTTTCAAAGATGTGTTGCTATCCTGAA AATTCTGTAGGTTCTGTGGAAGTTCCAGTGTTCT CTCTTATTCCACTTCGGTAGAGGATTTCTAGTTT CTTGTGGGCTAATTAAATAAATCATTAATACTCT TCTAATGGTCTTTGAATAAAGCCTGAGTAGGAA GTCTAGA | |
| 3UTR-005 | α-globin | GCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGC CCTTCTTCTCTCCCTTGCACCTGTACCTCTTGGTC TTTGAATAAAGCCTGAGTAGGAAGGCGGCCGCT CGAGCATGCATCTAGA | 9 |
| 3UTR-006 | G-CSF | GCCAAGCCCTCCCCATCCCATGTATTTATCTCTA TTTAATATTTATGTCTATTTAAGCCTCATATTTAA AGACAGGGAAGAGCAGAACGGAGCCCCAGGCC TCTGTGTCCTTCCCTGCATTTCTGAGTTTCATTCT CCTGCCTGTAGCAGTGAGAAAAAGCTCCTGTCCT CCCATCCCCTGGACTGGGAGGTAGATAGGTAAA TACCAAGTATTTATTACTATGACTGCTCCCCAGC CCTGGCTCTGCAATGGGCACTGGGATGAGCCGC TGTGAGCCCCTGGTCCTGAGGGTCCCCACCTGGG ACCCTTGAGAGTATCAGGTCTCCCACGTGGGAG ACAAGAAATCCCTGTTTAATATTTAAACAGCAGT GTTCCCCATCTGGGTCCTTGCACCCCTCACTCTG GCCTCAGCCGACTGCACAGCGGCCCCTGCATCC CCTTGGCTGTGAGGCCCCTGGACAAGCAGAGGT GGCCAGAGCTGGGAGGCATGGCCCTGGGGTCCC ACGAATTTGCTGGGGAATCTCGTTTTTCTTCTTA AGACTTTTGGGACATGGTTTGACTCCCGAACATC ACCGACGCGTCTCCTGTTTTTCTGGGTGGCCTCG GGACACCTGCCCTGCCCCCACGAGGGTCAGGAC TGTGACTCTTTTTAGGGCCAGGCAGGTGCCTGGA CATTTGCCTTGCTGGACGGGGACTGGGGATGTG GGAGGGAGCAGACAGGAGGAATCATGTCAGGC CTGTGTGTGAAAGGAAGCTCCACTGTCACCCTCC ACCTCTTCACCCCCCACTCACCAGTGTCCCCTCC ACTGTCACATTGTAACTGAACTTCAGGATAATAA AGTGTTTGCCTCCATGGTCTTTGAATAAAGCCTG AGTAGGAAGGCGGCCGCTCGAGCATGCATCTAG A | 10 |
| 3UTR-007 | Col1a2; collagen, type I, alpha 2 | ACTCAATCTAAATTAAAAAAGAAAGAAATTTGA AAAAACTTTCTCTTTGCCATTTCTTCTTCTTCTTT TTTAACTGAAAGCTGAATCCTTCCATTTCTTCTG CACATCTACTTGCTTAAATTGTGGGCAAAAGAG AAAAAGAAGGATTGATCAGAGCATTGTGCAATA CAGTTTCATTAACTCCTTCCCCCGCTCCCCCAAA AATTTGAATTTTTTTTTCAACACTCTTACACCTGT TATGGAAAATGTCAACCTTTGTAAGAAAACCAA AATAAAAATTGAAAAATAAAAACCATAAACATT TGCACCACTTGTGGCTTTTGAATATCTTCCACAG | 11 |

| | | | |
|---|---|---|---|
| | | AGGGAAGTTTAAAACCCAAACTTCCAAAGGTTT<br>AAACTACCTCAAAACACTTTCCCATGAGTGTGAT<br>CCACATTGTTAGGTGCTGACCTAGACAGAGATG<br>AACTGAGGTCCTTGTTTTGTTTTGTTCATAATAC<br>AAAGGTGCTAATTAATAGTATTTCAGATACTTGA<br>AGAATGTTGATGGTGCTAGAAGAATTTGAGAAG<br>AAATACTCCTGTATTGAGTTGTATCGTGTGGTGT<br>ATTTTTTAAAAAATTTGATTTAGCATTCATATTTT<br>CCATCTTATTCCCAATTAAAAGTATGCAGATTAT<br>TTGCCCAAATCTTCTTCAGATTCAGCATTTGTTCT<br>TTGCCAGTCTCATTTTCATCTTCTTCCATGGTTCC<br>ACAGAAGCTTTGTTTCTTGGGCAAGCAGAAAAA<br>TTAAATTGTACCTATTTTGTATATGTGAGATGTT<br>TAAATAAATTGTGAAAAAAATGAAATAAAGCAT<br>GTTTGGTTTTCCAAAAGAACATAT | |
| 3UTR-008 | Col6a2; collagen, type VI, alpha 2 | CGCCGCCGCCCGGGCCCCGCAGTCGAGGGTCGT<br>GAGCCCACCCCGTCCATGGTGCTAAGCGGGCCC<br>GGGTCCCACACGGCCAGCACCGCTGCTCACTCG<br>GACGACGCCCTGGGCCTGCACCTCTCCAGCTCCT<br>CCCACGGGGTCCCCGTAGCCCCGGCCCCCGCCC<br>AGCCCCAGGTCTCCCCAGGCCCTCCGCAGGCTG<br>CCCGGCCTCCCTCCCCCTGCAGCCATCCCAAGGC<br>TCCTGACCTACCTGGCCCCTGAGCTCTGGAGCAA<br>GCCCTGACCCAATAAAGGCTTTGAACCCAT | 12 |
| 3UTR-009 | RPN1; ribophorin I | GGGGCTAGAGCCCTCTCCGCACAGCGTGGAGAC<br>GGGGCAAGGAGGGGGGTTATTAGGATTGGTGGT<br>TTTGTTTTGCTTTGTTTAAAGCCGTGGGAAAATG<br>GCACAACTTTACCTCTGTGGGAGATGCAACACT<br>GAGAGCCAAGGGGTGGGAGTTGGGATAATTTTT<br>ATATAAAAGAAGTTTTTCCACTTTGAATTGCTAA<br>AAGTGGCATTTTTCCTATGTGCAGTCACTCCTCT<br>CATTTCTAAAATAGGGACGTGGCCAGGCACGGT<br>GGCTCATGCCTGTAATCCCAGCACTTTGGGAGGC<br>CGAGGCAGGCGGCTCACGAGGTCAGGAGATCGA<br>GACTATCCTGGCTAACACGGTAAAACCCTGTCTC<br>TACTAAAAGTACAAAAAATTAGCTGGGCGTGGT<br>GGTGGGCACCTGTAGTCCCAGCTACTCGGGAGG<br>CTGAGGCAGGAGAAAGGCATGAATCCAAGAGG<br>CAGAGCTTGCAGTGAGCTGAGATCACGCCATTG<br>CACTCCAGCCTGGGCAACAGTGTTAAGACTCTGT<br>CTCAAATATAAATAAATAAATAAATAAATAAAT<br>AAATAAATAAAAATAAAGCGAGATGTTGCCCTC<br>AAA | 13 |
| 3UTR-010 | LRP1; low density lipoprotein receptor-related protein 1 | GGCCCTGCCCCGTCGGACTGCCCCCAGAAAGCC<br>TCCTGCCCCCTGCCAGTGAAGTCCTTCAGTGAGC<br>CCCTCCCCAGCCAGCCCTTCCCTGGCCCCGCCGG<br>ATGTATAAATGTAAAAATGAAGGAATTACATTT<br>TATATGTGAGCGAGCAAGCCGGCAAGCGAGCAC<br>AGTATTATTTCTCCATCCCCTCCCTGCCTGCTCCT<br>TGGCACCCCCATGCTGCCTTCAGGGAGACAGGC<br>AGGGAGGGCTTGGGGCTGCACCTCCTACCCTCC | 14 |

| | | | |
|---|---|---|---|
| | | CACCAGAACGCACCCCACTGGGAGAGCTGGTGG<br>TGCAGCCTTCCCCTCCCTGTATAAGACACTTTGC<br>CAAGGCTCTCCCCTCTCGCCCCATCCCTGCTTGC<br>CCGCTCCCACAGCTTCCTGAGGGCTAATTCTGGG<br>AAGGGAGAGTTCTTTGCTGCCCCTGTCTGGAAG<br>ACGTGGCTCTGGGTGAGGTAGGCGGGAAAGGAT<br>GGAGTGTTTTAGTTCTTGGGGGAGGCCACCCCA<br>AACCCCAGCCCCAACTCCAGGGGCACCTATGAG<br>ATGGCCATGCTCAACCCCCCTCCCAGACAGGCC<br>CTCCCTGTCTCCAGGGCCCCCACCGAGGTTCCCA<br>GGGCTGGAGACTTCCTCTGGTAAACATTCCTCCA<br>GCCTCCCCTCCCCTGGGGACGCCAAGGAGGTGG<br>GCCACACCCAGGAAGGGAAAGCGGGCAGCCCC<br>GTTTTGGGGACGTGAACGTTTTAATAATTTTTGC<br>TGAATTCCTTTACAACTAAATAACACAGATATTG<br>TTATAAATAAAATTGT | |
| 3UTR-011 | Nnt1; cardiotrophin-like cytokine factor 1 | ATATTAAGGATCAAGCTGTTAGCTAATAATGCC<br>ACCTCTGCAGTTTTGGGAACAGGCAAATAAAGT<br>ATCAGTATACATGGTGATGTACATCTGTAGCAA<br>AGCTCTTGGAGAAAATGAAGACTGAAGAAAGCA<br>AAGCAAAAACTGTATAGAGAGATTTTTCAAAAG<br>CAGTAATCCCTCAATTTTAAAAAAGGATTGAAA<br>ATTCTAAATGTCTTTCTGTGCATATTTTTTGTGTT<br>AGGAATCAAAAGTATTTTATAAAAGGAGAAAGA<br>ACAGCCTCATTTTAGATGTAGTCCTGTTGGATTT<br>TTTATGCCTCCTCAGTAACCAGAAATGTTTTAAA<br>AAACTAAGTGTTTAGGATTTCAAGACAACATTAT<br>ACATGGCTCTGAAATATCTGACACAATGTAAAC<br>ATTGCAGGCACCTGCATTTTATGTTTTTTTTTTCA<br>ACAAATGTGACTAATTTGAAACTTTTATGAACTT<br>CTGAGCTGTCCCCTTGCAATTCAACCGCAGTTTG<br>AATTAATCATATCAAATCAGTTTTAATTTTTTAA<br>ATTGTACTTCAGAGTCTATATTTCAAGGGCACAT<br>TTTCTCACTACTATTTTAATACATTAAAGGACTA<br>AATAATCTTTCAGAGATGCTGGAAACAAATCAT<br>TTGCTTTATATGTTTCATTAGAATACCAATGAAA<br>CATACAACTTGAAAATTAGTAATAGTATTTTTGA<br>AGATCCCATTTCTAATTGGAGATCTCTTTAATTT<br>CGATCAACTTATAATGTGTAGTACTATATTAAGT<br>GCACTTGAGTGGAATTCAACATTTGACTAATAA<br>AATGAGTTCATCATGTTGGCAAGTGATGTGGCA<br>ATTATCTCTGGTGACAAAAGAGTAAAATCAAAT<br>ATTTCTGCCTGTTACAAATATCAAGGAAGACCTG<br>CTACTATGAAATAGATGACATTAATCTGTCTTCA<br>CTGTTTATAATACGGATGGATTTTTTTTCAAATC<br>AGTGTGTGTTTTGAGGTCTTATGTAATTGATGAC<br>ATTTGAGAGAAATGGTGGCTTTTTTTAGCTACCT<br>CTTTGTTCATTTAAGCACCAGTAAAGATCATGTC<br>TTTTTATAGAAGTGTAGATTTTCTTTGTGACTTTG<br>CTATCGTGCCTAAAGCTCTAAATATAGGTGAATG<br>TGTGATGAATACTCAGATTATTTGTCTCTCTATA | 15 |

| | | | |
|---|---|---|---|
| | | TAATTAGTTTGGTACTAAGTTTCTCAAAAAATTA<br>TTAACACATGAAAGACAATCTCTAAACCAGAAA<br>AAGAAGTAGTACAAATTTTGTTACTGTAATGCTC<br>GCGTTTAGTGAGTTTAAAACACACAGTATCTTTT<br>GGTTTTATAATCAGTTTCTATTTTGCTGTGCCTGA<br>GATTAAGATCTGTGTATGTGTGTGTGTGTGTGTG<br>TGCGTTTGTGTGTTAAAGCAGAAAAGACTTTTTT<br>AAAAGTTTTAAGTGATAAATGCAATTTGTTAATT<br>GATCTTAGATCACTAGTAAACTCAGGGCTGAATT<br>ATACCATGTATATTCTATTAGAAGAAAGTAAAC<br>ACCATCTTTATTCCTGCCCTTTTTCTTCTCTCAAA<br>GTAGTTGTAGTTATATCTAGAAAGAAGCAATTTT<br>GATTTCTTGAAAAGGTAGTTCCTGCACTCAGTTT<br>AAACTAAAAATAATCATACTTGGATTTTATTTAT<br>TTTTGTCATAGTAAAAATTTTAATTTATATATATT<br>TTTATTTAGTATTATCTTATTCTTTGCTATTTGCC<br>AATCCTTTGTCATCAATTGTGTTAAATGAATTGA<br>AAATTCATGCCCTGTTCATTTTATTTTACTTTATT<br>GGTTAGGATATTTAAAGGATTTTTGTATATATAA<br>TTTCTTAAATTAATATTCCAAAAGGTTAGTGGAC<br>TTAGATTATAAATTATGGCAAAAATCTAAAAAC<br>AACAAAAATGATTTTTATACATTCTATTTCATTA<br>TTCCTCTTTTTCCAATAAGTCATACAATTGGTAG<br>ATATGACTTATTTTATTTTTGTATTATTCACTATA<br>TCTTTATGATATTTAAGTATAAATAATTAAAAAA<br>ATTTATTGTACCTTATAGTCTGTCACCAAAAAAA<br>AAAAATTATCTGTAGGTAGTGAAATGCTAATGTT<br>GATTTGTCTTTAAGGGCTTGTTAACTATCCTTTAT<br>TTTCTCATTTGTCTTAAATTAGGAGTTTGTGTTTA<br>AATTACTCATCTAAGCAAAAAATGTATATAAAT<br>CCCATTACTGGGTATATACCCAAAGGATTATAA<br>ATCATGCTGCTATAAAGACACATGCACACGTAT<br>GTTTATTGCAGCACTATTCACAATAGCAAAGACT<br>TGGAACCAACCCAAATGTCCATCAATGATAGAC<br>TTGATTAAGAAAATGTGCACATATACACCATGG<br>AATACTATGCAGCCATAAAAAAGGATGAGTTCA<br>TGTCCTTTGTAGGGACATGGATAAAGCTGGAAA<br>CCATCATTCTGAGCAAACTATTGCAAGGACAGA<br>AAACCAAACACTGCATGTTCTCACTCATAGGTG<br>GGAATTGAACAATGAGAACACTTGGACACAAGG<br>TGGGGAACACCACACACCAGGGCCTGTCATGGG<br>GTGGGGGGAGTGGGGAGGGATAGCATTAGGAG<br>ATATACCTAATGTAAATGATGAGTTAATGGGTG<br>CAGCACACCAACATGGCACATGTATACATATGT<br>AGCAAACCTGCACGTTGTGCACATGTACCCTAG<br>AACTTAAAGTATAATTAAAAAAAAAAAAGAAAAC<br>AGAAGCTATTTATAAAGAAGTTATTTGCTGAAAT<br>AAATGTGATCTTTCCCATTAAAAAAATAAAGAA<br>ATTTTGGGGTAAAAAAACACAATATATTGTATTC<br>TTGAAAAATTCTAAGAGAGTGGATGTGAAGTGT<br>TCTCACCACAAAAGTGATAACTAATTGAGGTAA | |

| | | | |
|---|---|---|---|
| | | TGCACATATTAATTAGAAAGATTTTGTCATTCCA<br>CAATGTATATATACTTAAAAATATGTTATACACA<br>ATAAATACATACATTAAAAAATAAGTAAATGTA | |
| 3UTR-012 | Col6a1; collagen, type VI, alpha 1 | CCCACCCTGCACGCCGGCACCAAACCCTGTCCTC<br>CCACCCCTCCCCACTCATCACTAAACAGAGTAA<br>AATGTGATGCGAATTTTCCCGACCAACCTGATTC<br>GCTAGATTTTTTTTAAGGAAAAGCTTGGAAAGCC<br>AGGACACAACGCTGCTGCCTGCTTTGTGCAGGG<br>TCCTCCGGGGCTCAGCCCTGAGTTGGCATCACCT<br>GCGCAGGGCCCTCTGGGGCTCAGCCCTGAGCTA<br>GTGTCACCTGCACAGGGCCCTCTGAGGCTCAGC<br>CCTGAGCTGGCGTCACCTGTGCAGGGCCCTCTGG<br>GGCTCAGCCCTGAGCTGGCCTCACCTGGGTTCCC<br>CACCCCGGGCTCTCCTGCCCTGCCCTCCTGCCCG<br>CCCTCCCTCCTGCCTGCGCAGCTCCTTCCCTAGG<br>CACCTCTGTGCTGCATCCCACCAGCCTGAGCAAG<br>ACGCCCTCTCGGGGCCTGTGCCGCACTAGCCTCC<br>CTCTCCTCTGTCCCCATAGCTGGTTTTTCCCACCA<br>ATCCTCACCTAACAGTTACTTTACAATTAAACTC<br>AAAGCAAGCTCTTCTCCTCAGCTTGGGGCAGCC<br>ATTGGCCTCTGTCTCGTTTTGGGAAACCAAGGTC<br>AGGAGGCCGTTGCAGACATAAATCTCGGCGACT<br>CGGCCCCGTCTCCTGAGGGTCCTGCTGGTGACCG<br>GCCTGGACCTTGGCCCTACAGCCCTGGAGGCCG<br>CTGCTGACCAGCACTGACCCCGACCTCAGAGAG<br>TACTCGCAGGGGCGCTGGCTGCACTCAAGACCC<br>TCGAGATTAACGGTGCTAACCCCGTCTGCTCCTC<br>CCTCCCGCAGAGACTGGGGCCTGGACTGGACAT<br>GAGAGCCCCTTGGTGCCACAGAGGGCTGTGTCT<br>TACTAGAAACAACGCAAACCTCTCCTTCCTCAGA<br>ATAGTGATGTGTTCGACGTTTTATCAAAGGCCCC<br>CTTTCTATGTTCATGTTAGTTTTGCTCCTTCTGTG<br>TTTTTTTCTGAACCATATCCATGTTGCTGACTTTT<br>CCAAATAAAGGTTTTCACTCCTCTC | 16 |
| 3UTR-013 | Calr; calreticulin | AGAGGCCTGCCTCCAGGGCTGGACTGAGGCCTG<br>AGCGCTCCTGCCGCAGAGCTGGCCGCGCCAAAT<br>AATGTCTCTGTGAGACTCGAGAACTTTCATTTTT<br>TTCCAGGCTGGTTCGGATTTGGGGTGGATTTTGG<br>TTTTGTTCCCCTCCTCCACTCTCCCCCACCCCCTC<br>CCCGCCCTTTTTTTTTTTTTTTTTTAAACTGGTAT<br>TTTATCTTTGATTCTCCTTCAGCCCTCACCCCTGG<br>TTCTCATCTTTCTTGATCAACATCTTTTCTTGCCT<br>CTGTCCCCTTCTCTCATCTCTTAGCTCCCCTCCAA<br>CCTGGGGGGCAGTGGTGTGGAGAAGCCACAGGC<br>CTGAGATTTCATCTGCTCTCCTTCCTGGAGCCCA<br>GAGGAGGGCAGCAGAAGGGGGTGGTGTCTCCAA<br>CCCCCCAGCACTGAGGAAGAACGGGGCTCTTCT<br>CATTTCACCCCTCCCTTTCTCCCCTGCCCCCAGG<br>ACTGGGCCACTTCTGGGTGGGGCAGTGGGTCCC<br>AGATTGGCTCACACTGAGAATGTAAGAACTACA<br>AACAAAATTTCTATTAAATTAAATTTTGTGTCTC | 17 |

| | | | |
|---|---|---|---|
| | | C | |
| 3UTR-014 | Col1a1; collagen, type I, alpha 1 | CTCCCTCCATCCCAACCTGGCTCCCTCCCACCCA<br>ACCAACTTTCCCCCCAACCCGGAAACAGACAAG<br>CAACCCAAACTGAACCCCCTCAAAAGCCAAAAA<br>ATGGGAGACAATTTCACATGGACTTTGGAAAAT<br>ATTTTTTTCCTTTGCATTCATCTCTCAAACTTAGT<br>TTTTATCTTTGACCAACCGAACATGACCAAAAAC<br>CAAAAGTGCATTCAACCTTACCAAAAAAAAAAAA<br>AAAAAAAAGAATAAATAAATAACTTTTTAAAAA<br>AGGAAGCTTGGTCCACTTGCTTGAAGACCCATG<br>CGGGGGTAAGTCCCTTTCTGCCCGTTGGGCTTAT<br>GAAACCCCAATGCTGCCCTTTCTGCTCCTTTCTC<br>CACACCCCCCTTGGGGCCTCCCCTCCACTCCTTC<br>CCAAATCTGTCTCCCCAGAAGACACAGGAAACA<br>ATGTATTGTCTGCCCAGCAATCAAAGGCAATGCT<br>CAAACACCCAAGTGGCCCCCACCCTCAGCCCGC<br>TCCTGCCCGCCCAGCACCCCCAGGCCCTGGGGG<br>ACCTGGGGTTCTCAGACTGCCAAAGAAGCCTTG<br>CCATCTGGCGCTCCCATGGCTCTTGCAACATCTC<br>CCCTTCGTTTTTGAGGGGGTCATGCCGGGGGAGC<br>CACCAGCCCCTCACTGGGTTCGGAGGAGAGTCA<br>GGAAGGGCCACGACAAAGCAGAAACATCGGATT<br>TGGGGAACGCGTGTCAATCCCTTGTGCCGCAGG<br>GCTGGGCGGGAGAGACTGTTCTGTTCCTTGTGTA<br>ACTGTGTTGCTGAAAGACTACCTCGTTCTTGTCT<br>TGATGTGTCACCGGGGCAACTGCCTGGGGGCGG<br>GGATGGGGGCAGGGTGGAAGCGGCTCCCCATTT<br>TATACCAAAGGTGCTACATCTATGTGATGGGTG<br>GGGTGGGGAGGGAATCACTGGTGCTATAGAAAT<br>TGAGATGCCCCCCCAGGCCAGCAAATGTTCCTTT<br>TTGTTCAAAGTCTATTTTTATTCCTTGATATTTTT<br>CTTTTTTTTTTTTTTTTTTTGTGGATGGGGACTTG<br>TGAATTTTTCTAAAGGTGCTATTTAACATGGGAG<br>GAGAGCGTGTGCGGCTCCAGCCCAGCCCGCTGC<br>TCACTTTCCACCCTCTCTCCACCTGCCTCTGGCTT<br>CTCAGGCCTCTGCTCTCCGACCTCTCTCCTCTGA<br>AACCCTCCTCCACAGCTGCAGCCCATCCTCCCGG<br>CTCCCTCCTAGTCTGTCCTGCGTCCTCTGTCCCCG<br>GGTTTCAGAGACAACTTCCCAAAGCACAAAGCA<br>GTTTTTCCCCCTAGGGGTGGGAGGAAGCAAAAG<br>ACTCTGTACCTATTTTGTATGTGTATAATAATTT<br>GAGATGTTTTTAATTATTTTGATTGCTGGAATAA<br>AGCATGTGGAAATGACCCAAACATAATCCGCAG<br>TGGCCTCCTAATTTCCTTCTTTGGAGTTGGGGGA<br>GGGGTAGACATGGGGAAGGGGCTTTGGGGTGAT<br>GGGCTTGCCTTCCATTCCTGCCCTTTCCCTCCCCA<br>CTATTCTCTTCTAGATCCCTCCATAACCCCACTC<br>CCCTTTCTCTCACCCTTCTTATACCGCAAACCTTT<br>CTACTTCCTCTTTCATTTTCTATTCTTGCAATTTC<br>CTTGCACCTTTTCCAAATCCTCTTCTCCCCTGCAA<br>TACCATACAGGCAATCCACGTGCACAACACACA | 18 |

| | | | |
|---|---|---|---|
| | | CACACACTCTTCACATCTGGGGTTGTCCAAACCT<br>CATACCCACTCCCCTTCAAGCCCATCCACTCTCC<br>ACCCCCTGGATGCCCTGCACTTGGTGGCGGTGG<br>GATGCTCATGGATACTGGGAGGGTGAGGGGAGT<br>GGAACCCGTGAGGAGGACCTGGGGGCCTCTCCT<br>TGAACTGACATGAAGGGTCATCTGGCCTCTGCTC<br>CCTTCTCACCCACGCTGACCTCCTGCCGAAGGAG<br>CAACGCAACAGGAGAGGGGTCTGCTGAGCCTGG<br>CGAGGGTCTGGGAGGGACCAGGAGGAAGGCGT<br>GCTCCCTGCTCGCTGTCCTGGCCCTGGGGGAGTG<br>AGGGAGACAGACACCTGGGAGAGCTGTGGGGA<br>AGGCACTCGCACCGTGCTCTTGGGAAGGAAGGA<br>GACCTGGCCCTGCTCACCACGGACTGGGTGCCTC<br>GACCTCCTGAATCCCCAGAACACAACCCCCCTG<br>GGCTGGGGTGGTCTGGGGAACCATCGTGCCCCC<br>GCCTCCCGCCTACTCCTTTTTAAGCTT | |
| 3UTR-015 | Plod1; procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 | TTGGCCAGGCCTGACCCTCTTGGACCTTTCTTCT<br>TTGCCGACAACCACTGCCCAGCAGCCTCTGGGA<br>CCTCGGGGTCCCAGGGAACCCAGTCCAGCCTCC<br>TGGCTGTTGACTTCCCATTGCTCTTGGAGCCACC<br>AATCAAAGAGATTCAAAGAGATTCCTGCAGGCC<br>AGAGGCGGAACACACCTTTATGGCTGGGGCTCT<br>CCGTGGTGTTCTGGACCCAGCCCCTGGAGACAC<br>CATTCACTTTTACTGCTTTGTAGTGACTCGTGCTC<br>TCCAACCTGTCTTCCTGAAAAACCAAGGCCCCCT<br>TCCCCCACCTCTTCCATGGGGTGAGACTTGAGCA<br>GAACAGGGGCTTCCCCAAGTTGCCCAGAAAGAC<br>TGTCTGGGTGAGAAGCCATGGCCAGAGCTTCTC<br>CCAGGCACAGGTGTTGCACCAGGGACTTCTGCTT<br>CAAGTTTTGGGGTAAAGACACCTGGATCAGACT<br>CCAAGGGCTGCCCTGAGTCTGGGACTTCTGCCTC<br>CATGGCTGGTCATGAGAGCAAACCGTAGTCCCC<br>TGGAGACAGCGACTCCAGAGAACCTCTTGGGAG<br>ACAGAAGAGGCATCTGTGCACAGCTCGATCTTC<br>TACTTGCCTGTGGGGAGGGGAGTGACAGGTCCA<br>CACACCACACTGGGTCACCCTGTCCTGGATGCCT<br>CTGAAGAGAGGGACAGACCGTCAGAAACTGGA<br>GAGTTTCTATTAAAGGTCATTTAAACCA | 19 |
| 3UTR-016 | Nucb1; nucleobindin 1 | TCCTCCGGGACCCCAGCCCTCAGGATTCCTGATG<br>CTCCAAGGCGACTGATGGGCGCTGGATGAAGTG<br>GCACAGTCAGCTTCCCTGGGGGCTGGTGTCATGT<br>TGGGCTCCTGGGGCGGGGGCACGGCCTGGCATT<br>TCACGCATTGCTGCCACCCCAGGTCCACCTGTCT<br>CCACTTTCACAGCCTCCAAGTCTGTGGCTCTTCC<br>CTTCTGTCCTCCGAGGGGCTTGCCTTCTCTCGTG<br>TCCAGTGAGGTGCTCAGTGATCGGCTTAACTTAG<br>AGAAGCCCGCCCCCTCCCCTTCTCCGTCTGTCCC<br>AAGAGGGTCTGCTCTGAGCCTGCGTTCCTAGGTG<br>GCTCGGCCTCAGCTGCCTGGGTTGTGGCCGCCCT<br>AGCATCCTGTATGCCCACAGCTACTGGAATCCCC<br>GCTGCTGCTCCGGGCCAAGCTTCTGGTTGATTAA | 20 |

| | | | |
|---|---|---|---|
| | | TGAGGGCATGGGGTGGTCCCTCAAGACCTTCCC CTACCTTTTGTGGAACCAGTGATGCCTCAAAGAC AGTGTCCCCTCCACAGCTGGGTGCCAGGGGCAG GGGATCCTCAGTATAGCCGGTGAACCCTGATAC CAGGAGCCTGGGCCTCCCTGAACCCCTGGCTTCC AGCCATCTCATCGCCAGCCTCCTCCTGGACCTCT TGGCCCCCAGCCCCTTCCCCACACAGCCCCAGA AGGGTCCCAGAGCTGACCCCACTCCAGGACCTA GGCCCAGCCCCTCAGCCTCATCTGGAGCCCCTGA AGACCAGTCCCACCCACCTTTCTGGCCTCATCTG ACACTGCTCCGCATCCTGCTGTGTGTCCTGTTCC ATGTTCCGGTTCCATCCAAATACACTTTCTGGAA CAAA | |
| 3UTR-017 | α-globin | GCTGGAGCCTCGGTGGCCATGCTTCTTGCCCCTT GGGCCTCCCCCCAGCCCCTCCTCCCCTTCCTGCA CCCGTACCCCCGTGGTCTTTGAATAAAGTCTGAG TGGGCGGC | 21 |

**[00261]** It should be understood that those listed in the previous tables are examples and that any UTR from any gene may be incorporated into the respective first or second flanking region of the primary construct. Furthermore, multiple wild-type UTRs of any known gene may be utilized. It is also within the scope of the present invention to provide artificial UTRs which are not variants of wild type genes. These UTRs or portions thereof may be placed in the same orientation as in the transcript from which they were selected or may be altered in orientation or location. Hence a 5′ or 3′ UTR may be inverted, shortened, lengthened, made chimeric with one or more other 5′ UTRs or 3′ UTRs. As used herein, the term "altered" as it relates to a UTR sequence, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides. Any of these changes producing an "altered" UTR (whether 3′ or 5′) comprise a variant UTR.

**[00262]** In one embodiment, a double, triple or quadruple UTR such as a 5′ or 3′ UTR may be used. As used herein, a "double" UTR is one in which two copies of the same UTR are encoded either in series or substantially in series. For example, a double beta-globin 3′ UTR may be used as described in US Patent publication 20100129877, the contents of which are incorporated herein by reference in its entirety.

**[00263]** It is also within the scope of the present invention to have patterned UTRs. As used herein "patterned UTRs" are those UTRs which reflect a repeating or alternating pattern, such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than 3 times. In these patterns, each letter, A, B, or C represent a different UTR at the nucleotide level.

**[00264]** In one embodiment, flanking regions are selected from a family of transcripts whose proteins share a common function, structure, feature of property. For example, oncology-related polypeptides of interest may belong to a family of proteins which are expressed in a particular cell, tissue or at some time during development. The UTRs from any of these genes may be swapped for any other UTR of the same or different family of proteins to create a new chimeric primary transcript. As used herein, a "family of proteins" is used in the broadest sense to refer to a group of two or more oncology-related polypeptides of interest which share at least one function, structure, feature, localization, origin, or expression pattern.

**[00265]** After optimization (if desired), the signal-sensor primary construct components are reconstituted and transformed into a vector such as, but not limited to, plasmids, viruses, cosmids, and artificial chromosomes. For example, the optimized construct may be reconstituted and transformed into chemically competent *E. coli,* yeast, neurospora, maize, drosophila, etc. where high copy plasmid-like or chromosome structures occur by methods described herein.

*Stop Codons*

**[00266]** In one embodiment, the signal-sensor primary constructs of the present invention may include at least two stop codons before the 3' untranslated region (UTR). The stop codon may be selected from TGA, TAA and TAG. In one embodiment, the signal-sensor primary constructs of the present invention include the stop codon TGA and one additional stop codon. In a further embodiment the addition stop codon may be TAA.

*Vector Amplification*

**[00267]** The vector containing the signal-sensor primary construct is then amplified and the plasmid isolated and purified using methods known in the art such as, but not limited to, a maxi prep using the Invitrogen PURELINK™ HiPure Maxiprep Kit (Carlsbad, CA).

*Plasmid Linearization*

**[00268]** The plasmid may then be linearized using methods known in the art such as, but not limited to, the use of restriction enzymes and buffers. The linearization reaction may be purified using methods including, for example Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA), and HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC) and Invitrogen's standard PURELINK™ PCR Kit (Carlsbad, CA). The purification method may be modified depending on the size of the linearization reaction which was conducted. The linearized plasmid is then used to generate cDNA for *in vitro* transcription (IVT) reactions.

*cDNA Template Synthesis*

**[00269]** A cDNA template may be synthesized by having a linearized plasmid undergo polymerase chain reaction (PCR). Table 4 is a listing of primers and probes that may be useful in the PCR reactions of the present invention. It should be understood that the listing is not exhaustive and that primer-probe design for any amplification is within the skill of those in the art. Probes may also contain chemically modified bases to increase base-pairing fidelity to the target molecule and base-pairing strength. Such modifications may include 5-methyl-Cytidine, 2, 6-di-amino-purine, 2′-fluoro, phosphoro-thioate, or locked nucleic acids.

**Table 4. Primers and Probes**

| Primer/ Probe Identifier | Sequence (5′-3′) | Hybridization target | SEQ ID NO. |
|---|---|---|---|
| UFP | TTGGACCCTCGTACAGAAGCTAA TACG | cDNA Template | 22 |
| URP | $T_{x160}$CTTCCTACTCAGGCTTTATTC AAAGACCA | cDNA Template | 23 |
| GBA1 | CCTTGACCTTCTGGAACTTC | Acid glucocerebrosidase | 24 |
| GBA2 | CCAAGCACTGAAACGGATAT | Acid glucocerebrosidase | 25 |
| LUC1 | GATGAAAAGTGCTCCAAGGA | Luciferase | 26 |
| LUC2 | AACCGTGATGAAAAGGTACC | Luciferase | 27 |
| LUC3 | TCATGCAGATTGGAAAGGTC | Luciferase | 28 |

| | | | |
|---|---|---|---|
| GCSF1 | CTTCTTGGACTGTCCAGAGG | G-CSF | 29 |
| GCSF2 | GCAGTCCCTGATACAAGAAC | G-CSF | 30 |
| GCSF3 | GATTGAAGGTGGCTCGCTAC | G-CSF | 31 |

**[00270]** *UFP is universal forward primer; URP is universal reverse primer.

**[00271]** In one embodiment, the cDNA may be submitted for sequencing analysis before undergoing transcription.

*Signal-sensor polynucleotide Production (signal-sensor mRNA)*

**[00272]** The process of signal-sensor polynucleotide production may include, but is not limited to, *in vitro* transcription, cDNA template removal and RNA clean-up, and capping and/or tailing reactions.

*In Vitro Transcription*

**[00273]** The cDNA produced in the previous step may be transcribed using an *in vitro* transcription (IVT) system. The system typically comprises a transcription buffer, nucleotide triphosphates (NTPs), an RNase inhibitor and a polymerase. The NTPs may be manufactured in house, may be selected from a supplier, or may be synthesized as described herein. The NTPs may be selected from, but are not limited to, those described herein including natural and unnatural (modified) NTPs. The polymerase may be selected from, but is not limited to, T7 RNA polymerase, T3 RNA polymerase and mutant polymerases such as, but not limited to, polymerases able to be incorporated into modified nucleic acids.

*RNA Polymerases*

**[00274]** Any number of RNA polymerases or variants may be used in the design of the signal-sensor primary constructs of the present invention.

**[00275]** RNA polymerases may be modified by inserting or deleting amino acids of the RNA polymerase sequence. As a non-limiting example, the RNA polymerase may be modified to exhibit an increased ability to incorporate a 2'-modified nucleotide triphosphate compared to an unmodified RNA polymerase (see International Publication WO2008078180 and U.S. Patent 8,101,385; herein incorporated by reference in their entireties).

**[00276]** Variants may be obtained by evolving an RNA polymerase, optimizing the RNA polymerase amino acid and/or nucleic acid sequence and/or by using other methods known in the art. As a non-limiting example, T7 RNA polymerase variants may be evolved using the continuous directed evolution system set out by Esvelt *et al.* (Nature (2011) 472(7344):499-503; herein incorporated by reference in its entirety) where clones of T7 RNA polymerase may encode at least one mutation such as, but not limited to, lysine at position 93 substituted for threonine (K93T), I4M, A7T, E63V, V64D, A65E, D66Y, T76N, C125R, S128R, A136T, N165S, G175R, H176L, Y178H, F182L, L196F, G198V, D208Y, E222K, S228A, Q239R, T243N, G259D, M267I, G280C, H300R, D351A, A354S, E356D, L360P, A383V, Y385C, D388Y, S397R, M401T, N410S, K450R, P451T, G452V, E484A, H523L, H524N, G542V, E565K, K577E, K577M, N601S, S684Y, L699I, K713E, N748D, Q754R, E775K, A827V, D851N or L864F. As another non-limiting example, T7 RNA polymerase variants may encode at least mutation as described in U.S. Pub. Nos. 20100120024 and 20070117112; herein incorporated by reference in their entireties. Variants of RNA polymerase may also include, but are not limited to, substitutional variants, conservative amino acid substitution, insertional variants, deletional variants and/or covalent derivatives.

**[00277]** In one embodiment, the signal-sensor primary construct may be designed to be recognized by the wild type or variant RNA polymerases. In doing so, the signal-sensor primary construct may be modified to contain sites or regions of sequence changes from the wild type or parent primary construct.

**[00278]** In one embodiment, the signal-sensor primary construct may be designed to include at least one substitution and/or insertion upstream of an RNA polymerase binding or recognition site, downstream of the RNA polymerase binding or recognition site, upstream of the TATA box sequence, downstream of the TATA box sequence of the signal-sensor primary construct but upstream of the coding region of the primary construct, within the 5'UTR, before the 5'UTR and/or after the 5'UTR.

**[00279]** In one embodiment, the 5'UTR of the signal-sensor primary construct may be replaced by the insertion of at least one region and/or string of nucleotides of the same base. The region and/or string of nucleotides may include, but is not limited to, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 nucleotides and the nucleotides may

be natural and/or unnatural. As a non-limiting example, the group of nucleotides may include 5-8 adenine, cytosine, thymine, a string of any of the other nucleotides disclosed herein and/or combinations thereof.

**[00280]** In one embodiment, the 5'UTR of the signal-sensor primary construct may be replaced by the insertion of at least two regions and/or strings of nucleotides of two different bases such as, but not limited to, adenine, cytosine, thymine, any of the other nucleotides disclosed herein and/or combinations thereof. For example, the 5'UTR may be replaced by inserting 5-8 adenine bases followed by the insertion of 5-8 cytosine bases. In another example, the 5'UTR may be replaced by inserting 5-8 cytosine bases followed by the insertion of 5-8 adenine bases.

**[00281]** In one embodiment, the signal-sensor primary construct may include at least one substitution and/or insertion downstream of the transcription start site which may be recognized by an RNA polymerase. As a non-limiting example, at least one substitution and/or insertion may occur downstream the transcription start site by substituting at least one nucleic acid in the region just downstream of the transcription start site (such as, but not limited to, +1 to +6). Changes to region of nucleotides just downstream of the transcription start site may affect initiation rates, increase apparent nucleotide triphosphate (NTP) reaction constant values, and increase the dissociation of short transcripts from the transcription complex curing initial transcription (Brieba et al, Biochemistry (2002) 41: 5144-5149; herein incorporated by reference in its entirety). The modification, substitution and/or insertion of at least one nucleic acid may cause a silent mutation of the nucleic acid sequence or may cause a mutation in the amino acid sequence.

**[00282]** In one embodiment, the signal-sensor primary construct may include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12 or at least 13 guanine bases downstream of the transcription start site.

**[00283]** In one embodiment, the signal-sensor primary construct may include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 guanine bases in the region just downstream of the transcription start site. As a non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be

substituted by at least 1, at least 2, at least 3 or at least 4 adenine nucleotides. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be substituted by at least 1, at least 2, at least 3 or at least 4 cytosine bases. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be substituted by at least 1, at least 2, at least 3 or at least 4 thymine, and/or any of the nucleotides described herein.

**[00284]** In one embodiment, the signal-sensor primary construct may include at least one substitution and/or insertion upstream of the start codon. For the purpose of clarity, one of skill in the art would appreciate that the start codon is the first codon of the protein coding region whereas the transcription start site is the site where transcription begins. The signal-sensor primary construct may include, but is not limited to, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 substitutions and/or insertions of nucleotide bases. The nucleotide bases may be inserted or substituted at 1, at least 1, at least 2, at least 3, at least 4 or at least 5 locations upstream of the start codon. The nucleotides inserted and/or substituted may be the same base (e.g., all A or all C or all T or all G), two different bases (e.g., A and C, A and T, or C and T), three different bases (e.g., A, C and T or A, C and T) or at least four different bases. As a non-limiting example, the guanine base upstream of the coding region in the signal-sensor primary construct may be substituted with adenine, cytosine, thymine, or any of the nucleotides described herein. In another non-limiting example the substitution of guanine bases in the signal-sensor primary construct may be designed so as to leave one guanine base in the region downstream of the transcription start site and before the start codon (see Esvelt *et al.* Nature (2011) 472(7344):499-503; herein incorporated by reference in its entirety). As a non-limiting example, at least 5 nucleotides may be inserted at 1 location downstream of the transcription start site but upstream of the start codon and the at least 5 nucleotides may be the same base type.

*cDNA Template Removal and Clean-Up*

**[00285]** The cDNA template may be removed using methods known in the art such as, but not limited to, treatment with Deoxyribonuclease I (DNase I). RNA clean-up may also include a purification method such as, but not limited to, AGENCOURT® CLEANSEQ® system from Beckman Coulter (Danvers, MA), HPLC based purification

methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC) .

*Capping and/or Tailing Reactions*

**[00286]** The signal-sensor primary construct or mmRNA may also undergo capping and/or tailing reactions. A capping reaction may be performed by methods known in the art to add a 5′ cap to the 5′ end of the signal-sensor primary construct. Methods for capping include, but are not limited to, using a Vaccinia Capping enzyme (New England Biolabs, Ipswich, MA).

**[00287]** A poly-A tailing reaction may be performed by methods known in the art, such as, but not limited to, 2′ O-methyltransferase and by methods as described herein. If the signal-sensor primary construct generated from cDNA does not include a poly-T, it may be beneficial to perform the poly-A-tailing reaction before the signal-sensor primary construct is cleaned.

*Purification*

**[00288]** Signal-sensor primary construct or mmRNA purification may include, but is not limited to, mRNA or mmRNA clean-up, quality assurance and quality control. mRNA or mmRNA clean-up may be performed by methods known in the arts such as, but not limited to, AGENCOURT® beads (Beckman Coulter Genomics, Danvers, MA), poly-T beads, LNA™ oligo-T capture probes (EXIQON® Inc, Vedbaek, Denmark) or HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC). The term "purified" when used in relation to a polynucleotide such as a "purified mRNA or signal-sensor mmRNA" refers to one that is separated from at least one contaminant. As used herein, a "contaminant" is any substance which makes another unfit, impure or inferior. Thus, a purified signal-sensor polynucleotide (e.g., DNA and RNA) is present in a form or setting different from that in which it is found in nature, or a form or setting different from that which existed prior to subjecting it to a treatment or purification method.

**[00289]** A quality assurance and/or quality control check may be conducted using methods such as, but not limited to, gel electrophoresis, UV absorbance, or analytical HPLC.

**[00290]** In another embodiment, the signal-sensor mRNA or mmRNA may be sequenced by methods including, but not limited to reverse-transcriptase-PCR.

**[00291]** In one embodiment, the signal-sensor mRNA or mmRNA may be quantified using methods such as, but not limited to, ultraviolet visible spectroscopy (UV/Vis). A non-limiting example of a UV/Vis spectrometer is a NANODROP® spectrometer (ThermoFisher, Waltham, MA). The quantified signal-sensor mRNA or mmRNA may be analyzed in order to determine if the signal-sensor mRNA or mmRNA may be of proper size, check that no degradation of the signal-sensor mRNA or mmRNA has occurred. Degradation of the signal-sensor mRNA and/or mmRNA may be checked by methods such as, but not limited to, agarose gel electrophoresis, HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), liquid chromatography-mass spectrometry (LCMS), capillary electrophoresis (CE) and capillary gel electrophoresis (CGE).

*Signal Peptides or Proteins*

**[00292]** The signal-sensor primary constructs or mmRNA may also encode additional features which facilitate trafficking of the polypeptides to therapeutically relevant sites. One such feature which aids in protein trafficking is the signal peptide sequence. As used herein, a "signal sequence" or "signal peptide" is a polynucleotide or polypeptide, respectively, which is from about 9 to 200 nucleotides (3-60 amino acids) in length which is incorporated at the 5′ (or N-terminus) of the coding region or polypeptide encoded, respectively. Addition of these sequences result in trafficking of the encoded oncology-related polypeptide to the endoplasmic reticulum through one or more secretory pathways. Some signal peptides are cleaved from the protein by signal peptidase after the proteins are transported.

**[00293]** Table 5 is a representative listing of signal proteins or peptides which may be incorporated for encoding by the signal-sensor polynucleotides, primary constructs or mmRNA of the invention.

## Table 5. Signal Peptides

| ID | Description | NUCLEOTIDE SEQUENCE (5′-3′) | SEQ ID NO. | ENCODED PEPTIDE | SEQ ID NO. |
|---|---|---|---|---|---|
| SS-001 | α-1-antitrypsin | ATGATGCCATCCTCAGTCTCATGGGGTATTTTGCTCTTGGCGGGTCTGTGCTGTCTCGTGCCGGTGTCGCTCGCA | 32 | MMPSSVSWGILLAGLCCLVPVSLA | 94 |
| SS-002 | G-CSF | ATGGCCGGACCGGCGACTCAGTCGCCCATGAAACTCATGGCCCTGCAGTTGTTGCTTTGGCACTCAGCCCTCTGGACCGTCCAAGAGGCG | 33 | MAGPATQSPMKLMALQLLLWHSALWTVQEA | 95 |
| SS-003 | Factor IX | ATGCAGAGAGTGAACATGATTATGGCCGAGTCCCCATCGCTCATCACAATCTGCCTGCTTGGTACCTGCTTTCCGCCGAATGCACTGTCTTTCTGGATCACGAGAATGCGAATAAGATCTTGAACCGACCCAAACGG | 34 | MQRVNMIMAESPSLITICLLGYLLSAECTVFLDHENANKILNRPKR | 96 |
| SS-004 | Prolactin | ATGAAAGGATCATTGCTGTTGCTCCTCGTGTCGAACCTTCTGCTTTGCCAGTCCGTAGCCCCC | 35 | MKGSLLLLLVSNLLLCQSVAP | 97 |
| SS-005 | Albumin | ATGAAATGGGTGACGTTCATCTCACTGTTGTTTTTGTTCTCGTCCGCCTACTCCAGGGGAGTATTCCGCCGA | 36 | MKWVTFISLLFLFSSAYSRGVFRR | 98 |
| SS-006 | HMMSP38 | ATGTGGTGGCGGCTCTGGTGGCTGCTCCTGTTGCTCCTCTTGCTGTGGCCCATGGTGTGGGCA | 37 | MWWRLWWLLLLLLLLPMWA | 99 |
| MLS-001 | ornithine carbamoyltransferase | TGCTCTTTAACCTCCGCATCCTGTTGAATAACGCTGCGTTCCGAAATGGGCATAACTTCATGGTACGCAACTTCAGATGCGGCCAGCCACTCCAG | 38 | MLFNLRILLNNAAFRNGHNFMVRNFRCGQPLQ | 100 |
| MLS-002 | Cytochrome C Oxidase subunit 8A | ATGTCCGTCTTGACACCCCTGCTCTTGAGAGGGCTGACGGGGTCCGCTAGACGCCTGCCGGTACCGCGAGCGAAGATCCACTCCCTG | 39 | MSVLTPLLLRGLTGSARRLPVPRAKIHSL | 101 |
| MLS-003 | Cytochrome C Oxidase subunit 8A | ATGAGCGTGCTCACTCCGTTGCTTCTTCGAGGGCTTACGGGATCGGCTCGGAGGTTGCCCGTCCCGAGAGCGAAGATCCATTCGTTG | 40 | MSVLTPLLLRGLTGSARRLPVPRAKIHSL | 102 |
| SS-007 | Type III, bacterial | TGACAAAAATAACTTTATCTCCCCAGAATTTTAGAATCCAAAAACAGGAAACCACACTACTAAAAGAAAAATCAACCGAGAAAAATTCTTTAGCAAAAAGTAT | 41 | MVTKITLSPQNFRIQKQETTLLKEKSTEKNSLAKSILAVK | 103 |

| | | | | | |
|---|---|---|---|---|---|
| | | TCTCGCAGTAAAAATCACTTC ATCGAATTAAGGTCAAAATTA TCGGAACGTTTTATTTCGCAT AAGAACACT | | NHFIELRS KLSERFIS HKNT | |
| SS-008 | Viral | ATGCTGAGCTTTGTGGATACC CGCACCCTGCTGCTGCTGGCG GTGACCAGCTGCCTGGCGACC TGCCAG | 42 | MLSFVDT RTLLLLAV TSCLATCQ | 104 |
| SS-009 | viral | ATGGGCAGCAGCCAGGCGCC GCGCATGGGCAGCGTGGGCG GCCATGGCCTGATGGCGCTGC TGATGGCGGGCCTGATTCTGC CGGGCATTCTGGCG | 43 | MGSSQAP RMGSVGG HGLMALL MAGLILPG ILA | 105 |
| SS-010 | Viral | ATGGCGGGCATTTTTTATTTTC TGTTTAGCTTTCTGTTTGGCAT TTGCGAT | 44 | MAGIFYFL FSFLFGICD | 106 |
| SS-011 | Viral | ATGGAAAACCGCCTGCTGCGC GTGTTTCTGGTGTGGGCGGCG CTGACCATGGATGGCGCGAGC GCG | 45 | MENRLLR VFLVWAA LTMDGAS A | 107 |
| SS-012 | Viral | ATGGCGCGCCAGGGCTGCTTT GGCAGCTATCAGGTGATTAGC CTGTTTACCTTTGCGATTGGC GTGAACCTGTGCCTGGGC | 46 | MARQGCF GSYQVISL FTFAIGVN LCLG | 108 |
| SS-013 | *Bacillus* | ATGAGCCGCCTGCCGGTGCTG CTGCTGCTGCAGCTGCTGGTG CGCCCGGGCCTGCAG | 47 | MSRLPVLL LLQLLVRP GLQ | 109 |
| SS-014 | *Bacillus* | ATGAAACAGCAGAAACGCCT GTATGCGCGCCTGCTGACCCT GCTGTTTGCGCTGATTTTTCTG CTGCCGCATAGCAGCGCGAGC GCG | 48 | MKQQKRL YARLLTLL FALIFLLPH SSASA | 110 |
| SS-015 | Secretion signal | ATGGCGACGCCGCTGCCTCCG CCCTCCCCGCGGCACCTGCGG CTGCTGCGGCTGCTGCTCTCC GCCCTCGTCCTCGGC | 49 | MATPLPPP SPRHLRLL RLLLSG | 111 |
| SS-016 | Secretion signal | ATGAAGGCTCCGGGTCGGCTC GTGCTCATCATCCTGTGCTCC GTGGTCTTCTCT | 50 | MKAPGRL VLIILCSVV FS | 112 |
| SS-017 | Secretion signal | ATGCTTCAGCTTTGGAAACTT GTTCTCCTGTGCGGCGTGCTC ACT | 51 | MLQLWKL LCGVLT | 113 |
| SS-018 | Secretion signal | ATGCTTTATCTCCAGGGTTGG AGCATGCCTGCTGTGGCA | 52 | MLYLQGW SMPAVA | 114 |
| SS-019 | Secretion signal | ATGGATAACGTGCAGCCGAA AATAAAACATCGCCCCTTCTG CTTCAGTGTGAAAGGCCACGT GAAGATGCTGCGGCTGGATAT TATCAACTCACTGGTAACAAC AGTATTCATGCTCATCGTATC | 53 | MDNVQPK IKHRPFCF SVKGHVK MLRLDIIN SLVTTVFM LIVSVLALI | 115 |

| | | | | | |
|---|---|---|---|---|---|
| | | TGTGTTGGCACTGATACCA | | P | |
| SS-020 | Secretion signal | ATGCCCTGCCTAGACCAACAG CTCACTGTTCATGCCCTACCCT GCCCTGCCCAGCCCTCCTCTC TGGCCTTCTGCCAAGTGGGGT TCTTAACAGCA | 54 | MPCLDQQ LTVHALPC PAQPSSLA FCQVGFLT A | 116 |
| SS-021 | Secretion signal | ATGAAAACCTTGTTCAATCCA GCCCCTGCCATTGCTGACCTG GATCCCCAGTTCTACACCCTC TCAGATGTGTTCTGCTGCAAT GAAAGTGAGGCTGAGATTTTA ACTGGCCTCACGGTGGGCAGC GCTGCAGATGCT | 55 | MKTLFNP APAIADLD PQFYTLSD VFCCNESE AEILTGLT VGSAADA | 117 |
| SS-022 | Secretion signal | ATGAAGCCTCTCCTTGTTGTG TTTGTCTTTCTTTTCCTTTGGG ATCCAGTGCTGGCA | 56 | MKPLLVV FVFLFLWD PVLA | 118 |
| SS-023 | Secretion signal | ATGTCCTGTTCCCTAAAGTTT ACTTTGATTGTAATTTTTTTT ACTGTTGGCTTTCATCCAGC | 57 | MSCSLKFT LIVIFFTCT LSSS | 119 |
| SS-024 | Secretion signal | ATGGTTCTTACTAAACCTCTTC AAAGAAATGGCAGCATGATG AGCTTTGAAAATGTGAAAGAA AAGAGCAGAGAAGGAGGGCC CCATGCACACACACCCGAAGA AGAATTGTGTTTCGTGGTAAC ACACTACCCTCAGGTTCAGAC CACACTCAACCTGTTTTTCCAT ATATTCAAGGTTCTTACTCAA CCACTTTCCCTTCTGTGGGGT | 58 | MVLTKPL QRNGSMM SFENVKEK SREGGPHA HTPEEELC FVVTHTPQ VQTTLNLF FHIFKVLT QPLSLLW G | 120 |
| SS-025 | Secretion signal | ATGGCCACCCCGCCATTCCGG CTGATAAGGAAGATGTTTTCC TTCAAGGTGAGCAGATGGATG GGGCTTGCCTGCTTCCGGTCC CTGGCGGCATCC | 59 | MATPPFRL IRKMFSFK VSRWMGL ACFRSLAA S | 121 |
| SS-026 | Secretion signal | ATGAGCTTTTTCCAACTCCTG ATGAAAAGGAAGGAACTCAT TCCCTTGGTGGTGTTCATGAC TGTGGCGGCGGGTGGAGCCTC ATCT | 60 | MSFFQLL MKRKELIP LVVFMTV AAGGASS | 122 |
| SS-027 | Secretion signal | ATGGTCTCAGCTCTGCGGGGA GCACCCCTGATCAGGGTGCAC TCAAGCCCTGTTTCTTCTCCTT CTGTGAGTGGACCACGGAGGC TGGTGAGCTGCCTGTCATCCC AAAGCTCAGCTCTGAGC | 61 | MVSALRG APLIRVHS SPVSSPSV SGPAALVS CLSSQSSA LS | 123 |
| SS-028 | Secretion signal | ATGATGGGGTCCCCAGTGAGT CATCTGCTGGCCGGCTTCTGT GTGTGGGTCGTCTTGGGC | 62 | MMGSPVS HLLAGFC VWVVLG | 124 |
| SS-029 | Secretion signal | ATGGCAAGCATGGCTGCCGTG CTCACCTGGGCTCTGGCTCTT | 63 | MASMAAV LTWALAL | 125 |

| | | | | | |
|---|---|---|---|---|---|
| | | CTTTCAGCGTTTTCGGCCACC CAGGCA | | LSAFSATQ A | |
| SS-030 | Secretion signal | ATGGTGCTCATGTGGACCAGT GGTGACGCCTTCAAGACGGCC TACTTCCTGCTGAAGGGTGCC CCTCTGCAGTTCTCCGTGTGC GGCCTGCTGCAGGTGCTGGTG GACCTGGCCATCCTGGGGCAG GCCTACGCC | 64 | MVLMWTS GDAFKTA YFLLKGAP LQFSVCGL LQVLVDL AILGQATA | 126 |
| SS-031 | Secretion signal | ATGGATTTTGTCGCTGGAGCC ATCGGAGGCGTCTGCGGTGTT GCTGTGGGCTACCCCCTGGAC ACGGTGAAGGTCAGGATCCA GACGGAGCCAAAGTACACAG GCATCTGGCACTGCGTCCGGG ATACGTATCACCGAGAGCGCG TGTGGG GCTTCTACCGGGGCCTCTCGC TGCCCGTGTGCACGGTGTCCC TGGTATCTTCC | 65 | MDFVAGA IGGVCGV AVGYPLD TVKVRIQT EPLYTGIW HCVRDTY HRERVWG FYRGLSLP VCTVSLVS S | 127 |
| SS-032 | Secretion signal | ATGGAGAAGCCCCTCTTCCCA TTAGTGCCTTTGCATTGGTTTG GCTTTGGCTACACAGCACTGG TTGTTTCTGGTGGGATCGTTG GCTATGTAAAAACAGGCAGC GTGCCGTCCCTGGCTGCAGGG CTGCTCTTCGGCAGTCTAGCC | 66 | MEKPLFPL VPLHWFG FGYTALV VSGGIVGY VKTGSVPS LAAGLLFG SLA | 128 |
| SS-033 | Secretion signal | ATGGGTCTGCTCCTTCCCCTG GCACTCTGCATCCTAGTCCTG TGC | 67 | MGLLLPL ALCILVLC | 129 |
| SS-034 | Secretion signal | ATGGGGATCCAGACGAGCCCC GTCCTGCTGGCCTCCCTGGGG GTGGGGCTGGTCACTCTGCTC GGCCTGGCTGTGGGC | 68 | MGIQTSPV LLASLGVG LVTLLGLA VG | 130 |
| SS-035 | Secretion signal | ATGTCGGACCTGCTACTACTG GGCCTGATTGGGGGCCTGACT CTCTTACTGCTGCTGACGCTG CTAGCCTTTGCC | 69 | MSDLLLL GLIGGLTL LLLLTLLA FA | 131 |
| SS-036 | Secretion signal | ATGGAGACTGTGGTGATTGTT GCCATAGGTGTGCTGGCCACC ATGTTTCTGGCTTCGTTTGCAG CCTTGGTGCTGGTTTGCAGGC AG | 70 | METVVIV AIGVLATI FLASFAAL VLVCRQ | 132 |
| SS-037 | Secretion signal | ATGCGCGGCTCTGTGGAGTGC ACCTGGGGTTGGGGGCACTGT GCCCCCAGCCCCCTGCTCCTT TGGACTCTACTTCTGTTTGCA GCCCCATTTGGCCTGCTGGGG | 71 | MAGSVEC TWGWGH CAPSPLLL WTLLLFA APFGLLG | 133 |
| SS-038 | Secretion signal | ATGATGCCGTCCCGTACCAAC CTGGCTACTGGAATCCCCAGT | 72 | MMPSRTN LATGIPSS | 134 |

| | | | | | |
|---|---|---|---|---|---|
| | | AGTAAAGTGAAATATTCAAGGCTCTCCAGCACAGACGATGGCTACATTGACCTTCAGTTTAAGAAAACCCCTCCTAAGATCCCTTATAAGGCCATCGCACTTGCCACTGTGCTGTTTTTGATTGGCGCC | | KVKYSRLSSTDDGYIDLQFKKTPPKIPYKAIALATVLFLIGA | |
| SS-039 | Secretion signal | ATGGCCCTGCCCCAGATGTGTGACGGGAGCCACTTGGCCTCCACCCTCCGCTATTGCATGACAGTCAGCGGCACAGTGGTTCTGGTGGCCGGGACGCTCTGCTTCGCT | 73 | MALPQMCDGSHLASTLRYCMTVSGTVVLVAGTLCFA | 135 |
| SS-041 | Vrg-6 | TGAAAAAGTGGTTCGTTGCTGCCGGCATCGGCGCTGCCGGACTCATGCTCTCCAGCGCCGCCA | 74 | MKKWFVAAGIGAGLLMLSSAA | 136 |
| SS-042 | PhoA | ATGAAACAGAGCACCATTGCGCTGGCGCTGCTGCCGCTGCTGTTTACCCCGGTGACCAAAGCG | 75 | MKQSTIALALLPLLFTPVTKA | 137 |
| SS-043 | OmpA | ATGAAAAAAACCGCGATTGCGATTGCGGTGGCGCTGGCGGGCTTTGCGACCGTGGCGCAGGCG | 76 | MKKTAIAIAVALAGFATVAQA | 138 |
| SS-044 | STI | ATGAAAAAACTGATGCTGGCGATTTTTTTTAGCGTGCTGAGCTTTCCGAGCTTTAGCCAGAGC | 77 | MKKLMLAIFFSVLSFPSFSQS | 139 |
| SS-045 | STII | ATGAAAAAAAACATTGCGTTTCTGCTGGCGAGCATGTTTGTGTTTAGCATTGCGACCAACGCGTATGCG | 78 | MKKNIAFLLASMFVFSIATNAYA | 140 |
| SS-046 | Amylase | ATGTTTGCGAAACGCTTTAAAACCAGCCTGCTGCCGCTGTTTGCGGGCTTTCTGCTGCTGTTTCATCTGGTGCTGGCGGGCCCGGCGGCGGCGAGC | 79 | MFAKRFKTSLLPLFAGFLLLFHLVLAGPAAAS | 141 |
| SS-047 | Alpha Factor | ATGCGCTTTCCGAGCATTTTTACCGCGGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG | 80 | MRFPSIFTAVLFAASSALA | 142 |
| SS-048 | Alpha Factor | ATGCGCTTTCCGAGCATTTTTACCACCGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG | 81 | MRFPSIFTTVLFAASSALA | 143 |
| SS-049 | Alpha Factor | ATGCGCTTTCCGAGCATTTTTACCAGCGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG | 82 | MRFPSIFTSVLFAASSALA | 144 |
| SS-050 | Alpha Factor | ATGCGCTTTCCGAGCATTTTTACCCATGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG | 83 | MRFPSIFTHVLFAASSALA | 145 |
| SS-051 | Alpha Factor | ATGCGCTTTCCGAGCATTTTTACCATTGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG | 84 | MRFPSIFTIVLFAASSALA | 146 |

| | | | | | |
|---|---|---|---|---|---|
| SS-052 | Alpha Factor | ATGCGCTTTCCGAGCATTTTT ACCTTTGTGCTGTTTGCGGCG AGCAGCGCGCTGGCG | 85 | MRFPSIFTF VLFAASSA LA | 147 |
| SS-053 | Alpha Factor | ATGCGCTTTCCGAGCATTTTT ACCGAAGTGCTGTTTGCGGCG AGCAGCGCGCTGGCG | 86 | MRFPSIFT EVLFAASS ALA | 148 |
| SS-054 | Alpha Factor | ATGCGCTTTCCGAGCATTTTT ACCGGCGTGCTGTTTGCGGCG AGCAGCGCGCTGGCG | 87 | MRFPSIFT GVLFAASS ALA | 149 |
| SS-055 | Endoglucan ase V | ATGCGTTCCTCCCCCCTCCTCC GCTCCGCCGTTGTGGCCGCCC TGCCGGTGTTGGCCCTTGCC | 88 | MRSSPLLR SAVVAAL PVLALA | 150 |
| SS-056 | Secretion signal | ATGGGCGCGGCGGCCGTGCGC TGGCACTTGTGCGTGCTGCTG GCCCTGGGCACACGCGGGCG GCTG | 89 | MGAAAVR WHLCVLL ALGTRGR L | 151 |
| SS-057 | Fungal | ATGAGGAGCTCCCTTGTGCTG TTCTTTGTCTCTGCGTGGACG GCCTTGGCCAG | 90 | MRSSLVLF FVSAWTA LA | 152 |
| SS-058 | Fibronectin | ATGCTCAGGGGTCCGGGACCC GGGCGGCTGCTGCTGCTAGCA GTCCTGTGCCTGGGGACATCG GTGCGCTGCACCGAAACCGGG AAGAGCAAGAGG | 91 | MLRGPGP GRLLLLAV LCLGTSVR CTETGKSK R | 153 |
| SS-059 | Fibronectin | ATGCTTAGGGGTCCGGGGCCC GGGCTGCTGCTGCTGGCCGTC CAGCTGGGGACAGCGGTGCCC TCCACG | 92 | MLRGPGP GLLLLAV QCLGTAV PSTGA | 154 |
| SS-060 | Fibronectin | ATGCGCCGGGGGGCCCTGACC GGGCTGCTCCTGGTCCTGTGC CTGAGTGTTGTGCTACGTGCA GCCCCCTCTGCAACAAGCAAG AAGCGCAGG | 93 | MRRGALT GLLLVLCL SVVLRAAP SATSKKRR | 155 |

**[00294]** In the table, SS is secretion signal and MLS is mitochondrial leader signal. The signal-sensor primary constructs or mmRNA of the present invention may be designed to encode any of the signal peptide sequences of SEQ ID NOs 94-155, or fragments or variants thereof. These sequences may be included at the beginning of the oncology-related polypeptide coding region, in the middle or at the terminus or alternatively into a flanking region. Further, any of the signal-sensor polynucleotide primary constructs of the present invention may also comprise one or more of the sequences defined by SEQ ID NOs 32-93. These may be in the first region or either flanking region.

**[00295]** Additional signal peptide sequences which may be utilized in the present invention include those taught in, for example, databases such as those found at http://www.signalpeptide.de/ or http://proline.bic.nus.edu.sg/spdb/. Those described in US Patents 8,124,379; 7,413,875 and 7,385,034 are also within the scope of the invention and the contents of each are incorporated herein by reference in their entirety.

**[00296]** In one embodiment, the signal-sensor polynucleotide, primary constructs or mmRNA may include a nucleic acid sequence encoding a nuclear localization signal (NLS) and/or a nuclear export signal (NES). In one aspect, a signal-sensor polynucleotide, primary constructs or mmRNA may include a nucleic acid sequence encoding a nuclear localization signal (NLS). The signal-sensor polynucleotide, primary construct or mmRNA encoding a NLS would be able to traffic an oncology related polypeptide into the nucleus and deliver a survival or death signal to the nuclear microenvironment. In another aspect, the signal-sensor polynucleotide, primary constructs or mmRNA may include a nucleic acid sequence encoding a nuclear export signal such as NES1 and/or NES2. As a nonlimiting example, the signal-sensor polynucleotide, primary constructs or mmRNA may encode a NES1, NES2 and a NLS signal and an oncology related polypeptide or a scambled sequence which is not translatable in order to interact with HIF1-alpha to alter the transcritome of the cancer cells.

*Target Selection*

**[00297]** According to the present invention, the signal-sensor primary constructs comprise at least a first region of linked nucleosides encoding at least one oncology-related polypeptide of interest. The oncology-related polypeptides of interest or "targets" or oncology-related proteins and oncology-related peptides of the present invention are listed in Table 6, Table 7 and Table 41. Oncology-related polypeptides may be divided into classes based on their function and area of cancer intervention. For example, the classes may include targets associated with (1) apoptosis or Survival signal imbalance (AS targets). These may be caspase dependent or caspase independent targets; (2) replicative potential or anti-senescence (CC/S targets); (3) metabolic stress including the involvement of acidosis or hypoxia ($O_2$ > 1%) (M targets); (4) immune response (I targets); and (5) DNA damage/protection (DDR targets).

**[00298]** Shown in Table 6, in addition to the name and description of the gene encoding the oncology-related polypeptide of interest are the ENSEMBL Transcript ID (ENST), the ENSEMBL Protein ID (ENSP), each present where applicable, and when available the optimized sequence ID (OPT. SEQ ID). The targets are also categorized by group where "AS" refers to targets involved in apoptotic signaling; "M" refers to targets involved in metabolic processes and "CC/S" refers to targets involved in cell cycle and senescense.

**Table 6. Oncology Related Targets**

| Cat. | Target | Target Description | ENST ID | Trans. SEQ ID NO | ENSP ID | Prot. SEQ ID NO | OPT. SEQ ID NO |
|---|---|---|---|---|---|---|---|
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide | 238081 | 156 | 238081 | 1321 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, eta polypeptide | 248975 | 157 | 248975 | 1322 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide | 264335 | 158 | 264335 | 1323 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide | 307630 | 159 | 306330 | 1324 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 353245 | 160 | 309503 | 1325 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide | 353703 | 161 | 300161 | 1326 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide | 372839 | 162 | 361930 | 1327 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide | 381844 | 163 | 371267 | 1328 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 395948 | 164 | 379278 | 1329 | |
| AS | 14-3-3 | tyrosine 3- | 395951 | 165 | 379281 | 1330 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | | | | | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 395953 | 166 | 379283 | 1331 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 395956 | 167 | 379286 | 1332 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 395957 | 168 | 379287 | 1333 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 395958 | 169 | 379288 | 1334 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide | 414131 | 170 | 406058 | 1335 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 418997 | 171 | 416551 | 1336 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 419477 | 172 | 395114 | 1337 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide | 428262 | 173 | 394729 | 1338 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 437293 | 174 | 394880 | 1339 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide | 445830 | 175 | 394558 | 1340 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide | 446619 | 176 | 398990 | 1341 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide | 453207 | 177 | 390645 | 1342 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 457309 | 178 | 398599 | 1343 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 517797 | 179 | 427801 | 1344 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 521309 | 180 | 429623 | 1345 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 521328 | 181 | 429041 | 1346 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 521607 | 182 | 430058 | 1347 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 522542 | 183 | 430072 | 1348 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 522819 | 184 | 428775 | 1349 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 523131 | 185 | 428381 | 1350 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide | 523848 | 186 | 428860 | 1351 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, gamma polypeptide | 536755 | 187 | 443803 | 1352 | |
| AS | 14-3-3 | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, theta polypeptide | 539979 | 188 | 443226 | 1353 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 287295 | 189 | 287295 | 1354 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 2 | 307864 | 190 | 312370 | 1355 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 319908 | 191 | 315122 | 1356 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 333607 | 192 | 327671 | 1357 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 335375 | 193 | 335369 | 1358 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 346424 | 194 | 316320 | 1359 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 2 | 373248 | 195 | 362345 | 1360 | |
| AS | AIF | apoptosis-inducing factor, | 395039 | 196 | 378480 | 1361 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | mitochondrion-associated, 2 | | | | | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 399163 | 197 | 382116 | 1362 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 399167 | 198 | 382120 | 1363 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 405089 | 199 | 385800 | 1364 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 434714 | 200 | 399657 | 1365 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 440238 | 201 | 390798 | 1366 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 440263 | 202 | 405879 | 1367 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 3 | 441376 | 203 | 402067 | 1368 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 460436 | 204 | 431222 | 1369 | |
| AS | AIF | apoptosis-inducing factor, mitochondrion-associated, 1 | 535724 | 205 | 446113 | 1370 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) | 263826 | 206 | 263826 | 1371 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 311278 | 207 | 309428 | 1372 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) | 336199 | 208 | 336943 | 1373 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 349310 | 209 | 270202 | 1374 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 358335 | 210 | 351095 | 1375 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) | 366539 | 211 | 355497 | 1376 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) | 366540 | 212 | 355498 | 1377 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 391844 | 213 | 375719 | 1378 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 392037 | 214 | 375891 | 1379 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 392038 | 215 | 375892 | 1380 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 402615 | 216 | 385326 | 1381 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 407796 | 217 | 384293 | 1382 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 416362 | 218 | 407999 | 1383 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 416994 | 219 | 392458 | 1384 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 423127 | 220 | 403842 | 1385 | |
| AS | AKT | v-akt murine thymoma viral | 424901 | 221 | 399532 | 1386 | |

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|---|---|---|---|---|---|---|---|
| | (PKB) | oncogene homolog 2 | | | | | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 427375 | 222 | 403890 | 1387 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 452077 | 223 | 404083 | 1388 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 456441 | 224 | 396532 | 1389 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 2 | 537834 | 225 | 441591 | 1390 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 544168 | 226 | 443897 | 1391 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) | 552631 | 227 | 447820 | 1392 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 554581 | 228 | 451828 | 1393 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 554848 | 229 | 451166 | 1394 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 555528 | 230 | 450688 | 1395 | |
| AS | AKT (PKB) | v-akt murine thymoma viral oncogene homolog 1 | 555926 | 231 | 451824 | 1396 | |
| AS | ANT | solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4 | 281456 | 232 | 281456 | 1397 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 333991 | 233 | 334558 | 1398 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 339433 | 234 | 341830 | 1399 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 357310 | 235 | 349862 | 1400 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 359972 | 236 | 353059 | 1401 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 547045 | 237 | 449791 | 1402 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 549007 | 238 | 448161 | 1403 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 550527 | 239 | 448449 | 1404 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 551964 | 240 | 448165 | 1405 | |
| AS | Apaf-1 | apoptotic peptidase activating factor 1 | 552268 | 241 | 448826 | 1406 | |
| AS | APRIL( TNFSF13) | tumor necrosis factor (ligand) superfamily, member 13 | 338784 | 242 | 343505 | 1407 | |
| AS | APRIL( TNFSF13) | tumor necrosis factor (ligand) superfamily, member 13 | 349228 | 243 | 314455 | 1408 | |
| AS | APRIL( TNFSF13) | tumor necrosis factor (ligand) superfamily, member 13 | 380535 | 244 | 369908 | 1409 | |
| AS | APRIL( | tumor necrosis factor (ligand) | 396545 | 245 | 379794 | 1410 | |

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|---|---|---|---|---|---|---|---|
| | TNFSF13) | superfamily, member 13 | | | | | |
| AS | ARTS | phosphoribosyl pyrophosphate synthetase 1 | 372418 | 246 | 361495 | 1411 | |
| AS | ARTS | phosphoribosyl pyrophosphate synthetase 1 | 372419 | 247 | 361496 | 1412 | |
| AS | ARTS | phosphoribosyl pyrophosphate synthetase 1 | 372428 | 248 | 361505 | 1413 | |
| AS | ARTS | phosphoribosyl pyrophosphate synthetase 1 | 372435 | 249 | 361512 | 1414 | |
| AS | ARTS | phosphoribosyl pyrophosphate synthetase 1 | 543248 | 250 | 443185 | 1415 | |
| AS | ASK1 (MAP3K5) | mitogen-activated protein kinase kinase kinase 5 | 355845 | 251 | 348104 | 1416 | |
| AS | ASK1 (MAP3K5) | mitogen-activated protein kinase kinase kinase 5 | 359015 | 252 | 351908 | 1417 | |
| AS | ASK1 (MAP3K5) | mitogen-activated protein kinase kinase kinase 5 | 367768 | 253 | 356742 | 1418 | |
| AS | BAD | BCL2-associated agonist of cell death | 309032 | 254 | 309103 | 1419 | |
| AS | BAD | BCL2-associated agonist of cell death | 394532 | 255 | 378040 | 1420 | |
| AS | BAD | BCL2-associated agonist of cell death | 540152 | 256 | 440807 | 1421 | |
| AS | BAFF(TNFSF13B) | tumor necrosis factor (ligand) superfamily, member 13b | 375887 | 257 | 365048 | 1422 | |
| AS | BAFF(TNFSF13B) | tumor necrosis factor (ligand) superfamily, member 13b | 430559 | 258 | 389540 | 1423 | |
| AS | BAFF(TNFSF13B) | tumor necrosis factor (ligand) superfamily, member 13b | 542136 | 259 | 445334 | 1424 | |
| AS | Bak | BCL2-antagonist/killer 1 | 360661 | 260 | 353878 | 1425 | |
| AS | Bak | BCL2-antagonist/killer 1 | 374460 | 261 | 363584 | 1426 | |
| AS | Bak | BCL2-antagonist/killer 1 | 374467 | 262 | 363591 | 1427 | |
| AS | Bak | BCL2-antagonist/killer 1 | 442998 | 263 | 391258 | 1428 | |
| AS | BAX | BCL2-associated X protein | 293288 | 264 | 293288 | 1429 | |
| AS | BAX | BCL2-associated X protein | 345358 | 265 | 263262 | 1430 | |
| AS | BAX | BCL2-associated X protein | 354470 | 266 | 346461 | 1431 | |
| AS | BAX | BCL2-associated X protein | 391871 | 267 | 375744 | 1432 | |
| AS | BAX | BCL2-associated X protein | 415969 | 268 | 389971 | 1433 | |
| AS | BAX | BCL2-associated X protein | 539787 | 269 | 441413 | 1434 | |
| AS | Bcl-2 | B-cell CLL/lymphoma 2 | 333681 | 270 | 329623 | 1435 | |
| AS | Bcl-2 | B-cell CLL/lymphoma 2 | 398117 | 271 | 381185 | 1436 | |
| AS | Bcl-2 | B-cell CLL/lymphoma 2 | 444484 | 272 | 404214 | 1437 | |
| AS | Bcl-B | BCL2-like 10 (apoptosis facilitator) | 260442 | 273 | 260442 | 1438 | |

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|---|---|---|---|---|---|---|---|
| AS | Bcl-W | BCL2-like 2 | 250405 | 274 | 250405 | 1439 | |
| AS | Bcl-W | BCL2-like 2 | 554635 | 275 | 451234 | 1440 | |
| AS | Bcl-W | BCL2-like 2 | 557236 | 276 | 451701 | 1441 | |
| AS | Bcl-W | BCL2-like 2 | 557579 | 277 | 452265 | 1442 | |
| AS | Bcl-XL | BCL2-like 1 | 307677 | 278 | 302564 | 1443 | |
| AS | Bcl-XL | BCL2-like 1 | 376055 | 279 | 365223 | 1444 | |
| AS | Bcl-XL | BCL2-like 1 | 376062 | 280 | 365230 | 1445 | |
| AS | Bcl-XL | BCL2-like 1 | 420488 | 281 | 390760 | 1446 | |
| AS | Bcl-XL | BCL2-like 1 | 420653 | 282 | 405563 | 1447 | |
| AS | Bcl-XL | BCL2-like 1 | 422920 | 283 | 411252 | 1448 | |
| AS | Bcl-XL | BCL2-like 1 | 439267 | 284 | 389688 | 1449 | |
| AS | Bcl-XL | BCL2-like 1 | 450273 | 285 | 406203 | 1450 | |
| AS | Bcl-XL | BCL2-like 1 | 456404 | 286 | 395545 | 1451 | |
| AS | BCMA | tumor necrosis factor receptor superfamily, member 17 | 53243 | 287 | 53243 | 1452 | |
| AS | BCMA | tumor necrosis factor receptor superfamily, member 17 | 396495 | 288 | 379753 | 1453 | |
| AS | BCMA | tumor necrosis factor receptor superfamily, member 17 | 435355 | 289 | 401782 | 1454 | |
| AS | BFL1 | BCL2-related protein A1 | 267953 | 290 | 267953 | 1455 | |
| AS | BFL1 | BCL2-related protein A1 | 335661 | 291 | 335250 | 1456 | |
| AS | Bid | BH3 interacting domain death agonist | 317361 | 292 | 318822 | 1457 | |
| AS | Bid | BH3 interacting domain death agonist | 342111 | 293 | 344594 | 1458 | |
| AS | Bid | BH3 interacting domain death agonist | 399765 | 294 | 382667 | 1459 | |
| AS | Bid | BH3 interacting domain death agonist | 399767 | 295 | 382669 | 1460 | |
| AS | Bid | BH3 interacting domain death agonist | 399774 | 296 | 382674 | 1461 | |
| AS | Bid | BH3 interacting domain death agonist | 551952 | 297 | 449236 | 1462 | |
| AS | Bik | BCL2-interacting killer (apoptosis-inducing) | 216115 | 298 | 216115 | 1463 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 308659 | 299 | 309226 | 1464 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 337565 | 300 | 338374 | 1465 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 357757 | 301 | 350398 | 1466 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 393252 | 302 | 376941 | 1467 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 393253 | 303 | 376942 | 1468 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 393256 | 304 | 376943 | 1469 | |
| AS | Bim | BCL2-like 11 (apoptosis facilitator) | 432179 | 305 | 411870 | 1470 | |
| AS | Bim | BCL2-like 11 (apoptosis | 452033 | 306 | 403666 | 1471 | |

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|---|---|---|---|---|---|---|---|
| | | facilitator) | | | | | |
| AS | BMF | Bcl2 modifying factor | 220446 | 307 | 220446 | 1472 | |
| AS | BMF | Bcl2 modifying factor | 354670 | 308 | 346697 | 1473 | |
| AS | BMF | Bcl2 modifying factor | 397573 | 309 | 380703 | 1474 | |
| AS | BMF | Bcl2 modifying factor | 431415 | 310 | 396511 | 1475 | |
| AS | BMF | Bcl2 modifying factor | 559701 | 311 | 453919 | 1476 | |
| AS | BMF | Bcl2 modifying factor | 561282 | 312 | 453522 | 1477 | |
| AS | BMF | Bcl2 modifying factor | 561360 | 313 | 453892 | 1478 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 342045 | 314 | 339371 | 1479 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 344773 | 315 | 343412 | 1480 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 361704 | 316 | 354699 | 1481 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 379623 | 317 | 368944 | 1482 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 379624 | 318 | 368945 | 1483 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 379632 | 319 | 368953 | 1484 | |
| AS | BRE | brain and reproductive organ-expressed (TNFRSF1A modulator) | 436924 | 320 | 392345 | 1485 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 323055 | 321 | 320580 | 1486 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 394853 | 322 | 378322 | 1487 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 394854 | 323 | 378323 | 1488 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 507176 | 324 | 422990 | 1489 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 512215 | 325 | 422781 | 1490 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 523694 | 326 | 429350 | 1491 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 525819 | 327 | 434599 | 1492 | |
| AS | Calcineurin A | protein phosphatase 3, catalytic subunit, alpha isozyme | 529324 | 328 | 431619 | 1493 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 353247 | 329 | 344132 | 1494 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 393136 | 330 | 376844 | 1495 | |
| AS | Caspase- | caspase 1, apoptosis-related | 415981 | 331 | 408446 | 1496 | |

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|---|---|---|---|---|---|---|---|
| | 1 | cysteine peptidase (interleukin 1, beta, convertase) | | | | | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 436863 | 332 | 410076 | 1497 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 446369 | 333 | 403260 | 1498 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 525825 | 334 | 434779 | 1499 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 526568 | 335 | 434250 | 1500 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 528974 | 336 | 434259 | 1501 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 529871 | 337 | 431947 | 1502 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 531166 | 338 | 434303 | 1503 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 533400 | 339 | 433138 | 1504 | |
| AS | Caspase-1 | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) | 534497 | 340 | 436875 | 1505 | |
| AS | Caspase-10 | caspase 10, apoptosis-related cysteine peptidase | 272879 | 341 | 272879 | 1506 | |
| AS | Caspase-10 | caspase 10, apoptosis-related cysteine peptidase | 286186 | 342 | 286186 | 1507 | |
| AS | Caspase-10 | caspase 10, apoptosis-related cysteine peptidase | 346817 | 343 | 237865 | 1508 | |
| AS | Caspase-10 | caspase 10, apoptosis-related cysteine peptidase | 360132 | 344 | 353250 | 1509 | |
| AS | Caspase-2 | caspase 2, apoptosis-related cysteine peptidase | 310447 | 345 | 312664 | 1510 | |
| AS | Caspase-2 | caspase 2, apoptosis-related cysteine peptidase | 350623 | 346 | 340030 | 1511 | |
| AS | Caspase-2 | caspase 2, apoptosis-related cysteine peptidase | 392923 | 347 | 376654 | 1512 | |
| AS | Caspase-3 | caspase 3, apoptosis-related cysteine peptidase | 308394 | 348 | 311032 | 1513 | |
| AS | Caspase-3 | caspase 3, apoptosis-related cysteine peptidase | 438467 | 349 | 390792 | 1514 | |
| AS | Caspase-3 | caspase 3, apoptosis-related cysteine peptidase | 447121 | 350 | 407142 | 1515 | |
| AS | Caspase-3 | caspase 3, apoptosis-related cysteine peptidase | 523916 | 351 | 428929 | 1516 | |
| AS | Caspase-4 | caspase 4, apoptosis-related cysteine peptidase | 355546 | 352 | 347741 | 1517 | |
| AS | Caspase-4 | caspase 4, apoptosis-related cysteine peptidase | 417440 | 353 | 401673 | 1518 | |

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|---|---|---|---|---|---|---|---|
| AS | Caspase-4 | caspase 4, apoptosis-related cysteine peptidase | 444739 | 354 | 388566 | 1519 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 260315 | 355 | 260315 | 1520 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 393139 | 356 | 376847 | 1521 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 393141 | 357 | 376849 | 1522 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 418434 | 358 | 398130 | 1523 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 444749 | 359 | 388365 | 1524 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 526056 | 360 | 436877 | 1525 | |
| AS | Caspase-5 | caspase 5, apoptosis-related cysteine peptidase | 531367 | 361 | 434471 | 1526 | |
| AS | Caspase-6 | caspase 6, apoptosis-related cysteine peptidase | 265164 | 362 | 265164 | 1527 | |
| AS | Caspase-6 | caspase 6, apoptosis-related cysteine peptidase | 352981 | 363 | 285333 | 1528 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 345633 | 364 | 298701 | 1529 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369315 | 365 | 358321 | 1530 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369316 | 366 | 358322 | 1531 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369318 | 367 | 358324 | 1532 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369319 | 368 | 358325 | 1533 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369321 | 369 | 358327 | 1534 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 369331 | 370 | 358337 | 1535 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 429617 | 371 | 400094 | 1536 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 442393 | 372 | 394482 | 1537 | |
| AS | Caspase-7 | caspase 7, apoptosis-related cysteine peptidase | 452490 | 373 | 398107 | 1538 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 264274 | 374 | 264274 | 1539 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 264275 | 375 | 264275 | 1540 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 323492 | 376 | 325722 | 1541 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 358485 | 377 | 351273 | 1542 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 392258 | 378 | 376087 | 1543 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 392259 | 379 | 376088 | 1544 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 392261 | 380 | 376089 | 1545 | |

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|---|---|---|---|---|---|---|---|
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 392263 | 381 | 376091 | 1546 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 392266 | 382 | 376094 | 1547 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 413726 | 383 | 397528 | 1548 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 429881 | 384 | 390641 | 1549 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 432109 | 385 | 412523 | 1550 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 440732 | 386 | 396869 | 1551 | |
| AS | Caspase-8 | caspase 8, apoptosis-related cysteine peptidase | 447616 | 387 | 388306 | 1552 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 333868 | 388 | 330237 | 1553 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 348549 | 389 | 255256 | 1554 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 375874 | 390 | 365034 | 1555 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 375890 | 391 | 365051 | 1556 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 440484 | 392 | 411304 | 1557 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 447522 | 393 | 396540 | 1558 | |
| AS | Caspase-9 | caspase 9, apoptosis-related cysteine peptidase | 546424 | 394 | 449584 | 1559 | |
| AS | CD27 | CD27 molecule | 266557 | 395 | 266557 | 1560 | |
| AS | CD30 | tumor necrosis factor receptor superfamily, member 8 | 263932 | 396 | 263932 | 1561 | |
| AS | CD30 | tumor necrosis factor receptor superfamily, member 8 | 413146 | 397 | 398337 | 1562 | |
| AS | CD30 | tumor necrosis factor receptor superfamily, member 8 | 417814 | 398 | 390650 | 1563 | |
| AS | CD30L | tumor necrosis factor (ligand) superfamily, member 8 | 223795 | 399 | 223795 | 1564 | |
| AS | CD40 | CD40 molecule, TNF receptor superfamily member 5 | 372278 | 400 | 361352 | 1565 | |
| AS | CD40L(TNFSF5) | CD40 ligand | 370628 | 401 | 359662 | 1566 | |
| AS | CD40L(TNFSF5) | CD40 ligand | 370629 | 402 | 359663 | 1567 | |
| AS | CD41 | CD40 molecule, TNF receptor superfamily member 5 | 372276 | 403 | 361350 | 1568 | |
| AS | CD42 | CD40 molecule, TNF receptor superfamily member 5 | 372285 | 404 | 361359 | 1569 | |
| AS | CD70(TNFSF7) | CD70 molecule | 245903 | 405 | 245903 | 1570 | |
| AS | CD70(TNFSF7) | CD70 molecule | 423145 | 406 | 395294 | 1571 | |
| AS | CDK1 | cyclin-dependent kinase 1 | 316629 | 407 | 325970 | 1572 | |

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|---|---|---|---|---|---|---|---|
| | (p34) | | | | | | |
| AS | CDK1 (p34) | cyclin-dependent kinase 1 | 373809 | 408 | 362915 | 1573 | |
| AS | CDK1 (p34) | cyclin-dependent kinase 1 | 395284 | 409 | 378699 | 1574 | |
| AS | CDK1 (p34) | cyclin-dependent kinase 1 | 448257 | 410 | 397973 | 1575 | |
| AS | CDK1 (p34) | cyclin-dependent kinase 1 | 519078 | 411 | 430665 | 1576 | |
| AS | CDK5 | cyclin-dependent kinase 5 | 485972 | 412 | 419782 | 1577 | |
| AS | CDK5R 1 (p35) | cyclin-dependent kinase 5, regulatory subunit 1 (p35) | 313401 | 413 | 318486 | 1578 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 309955 | 414 | 312455 | 1579 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 340870 | 415 | 339326 | 1580 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 343375 | 416 | 339391 | 1581 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 355558 | 417 | 347757 | 1582 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 395148 | 418 | 378580 | 1583 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 417748 | 419 | 412882 | 1584 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 423241 | 420 | 399420 | 1585 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 433445 | 421 | 391029 | 1586 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 441224 | 422 | 411897 | 1587 | |
| AS | c-FLIP(S) | CASP8 and FADD-like apoptosis regulator | 443227 | 423 | 413270 | 1588 | |
| AS | cIAP1 | baculoviral IAP repeat containing 3 | NA | 424 | NA | 1589 | 2488 |
| AS | c-IAP1 | baculoviral IAP repeat containing 3 | 263464 | 425 | 263464 | 1590 | |
| AS | c-IAP1 | baculoviral IAP repeat containing 3 | 532808 | 426 | 432907 | 1591 | |
| AS | cIAP2 | baculoviral IAP repeat containing 2 | NA | 427 | NA | 1592 | |
| AS | C-IAP2 | baculoviral IAP repeat containing 2 | 227758 | 428 | 227758 | 1593 | |
| AS | C-IAP2 | baculoviral IAP repeat containing 2 | 530675 | 429 | 431723 | 1594 | |
| AS | C-IAP2 | baculoviral IAP repeat containing 2 | 532672 | 430 | 434979 | 1595 | |
| AS | C-IAP2 | baculoviral IAP repeat containing 2 | 541741 | 431 | 440771 | 1596 | |
| AS | c-Jun | jun proto-oncogene | 371222 | 432 | 360266 | 1597 | |
| AS | c-Raf-1 | v-raf-1 murine leukemia viral oncogene homolog 1 | 251849 | 433 | 251849 | 1598 | |
| AS | c-Raf-1 | v-raf-1 murine leukemia viral oncogene homolog 1 | 442415 | 434 | 401888 | 1599 | |

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|---|---|---|---|---|---|---|---|
| AS | c-Raf-1 | v-raf-1 murine leukemia viral oncogene homolog 1 | 534997 | 435 | 441186 | 1600 | |
| AS | c-Raf-1 | v-raf-1 murine leukemia viral oncogene homolog 1 | 542177 | 436 | 443567 | 1601 | |
| AS | Cytochrome c | cytochrome c, somatic | 305786 | 437 | 307786 | 1602 | |
| AS | Cytochrome c | cytochrome c, somatic | 409409 | 438 | 386270 | 1603 | |
| AS | Cytochrome c | cytochrome c, somatic | 409764 | 439 | 387279 | 1604 | |
| AS | Cytochrome c | cytochrome c, somatic | 413447 | 440 | 416479 | 1605 | |
| AS | DAXX | death-domain associated protein | 266000 | 441 | 266000 | 1606 | |
| AS | DAXX | death-domain associated protein | 374542 | 442 | 363668 | 1607 | |
| AS | DAXX | death-domain associated protein | 383062 | 443 | 372539 | 1608 | |
| AS | DAXX | death-domain associated protein | 383194 | 444 | 372681 | 1609 | |
| AS | DAXX | death-domain associated protein | 399060 | 445 | 382014 | 1610 | |
| AS | DAXX | death-domain associated protein | 399344 | 446 | 382281 | 1611 | |
| AS | DAXX | death-domain associated protein | 414083 | 447 | 396876 | 1612 | |
| AS | DAXX | death-domain associated protein | 414272 | 448 | 409756 | 1613 | |
| AS | DAXX | death-domain associated protein | 419855 | 449 | 397612 | 1614 | |
| AS | DAXX | death-domain associated protein | 428268 | 450 | 408215 | 1615 | |
| AS | DAXX | death-domain associated protein | 429531 | 451 | 415898 | 1616 | |
| AS | DAXX | death-domain associated protein | 433482 | 452 | 404623 | 1617 | |
| AS | DAXX | death-domain associated protein | 436311 | 453 | 404376 | 1618 | |
| AS | DAXX | death-domain associated protein | 438332 | 454 | 411700 | 1619 | |
| AS | DAXX | death-domain associated protein | 440500 | 455 | 403986 | 1620 | |
| AS | DAXX | death-domain associated protein | 445009 | 456 | 394108 | 1621 | |
| AS | DAXX | death-domain associated protein | 446403 | 457 | 406008 | 1622 | |
| AS | DAXX | death-domain associated protein | 453407 | 458 | 408499 | 1623 | |
| AS | DAXX | death-domain associated protein | 453931 | 459 | 412433 | 1624 | |
| AS | DAXX | death-domain associated protein | 454197 | 460 | 412177 | 1625 | |
| AS | DAXX | death-domain associated protein | 455860 | 461 | 410772 | 1626 | |

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|---|---|---|---|---|---|---|---|
| AS | DAXX | death-domain associated protein | 547663 | 462 | 447115 | 1627 | |
| AS | DAXX | death-domain associated protein | 548604 | 463 | 448337 | 1628 | |
| AS | DAXX | death-domain associated protein | 550822 | 464 | 447861 | 1629 | |
| AS | DAXX | death-domain associated protein | 552944 | 465 | 447833 | 1630 | |
| AS | DcR3 | tumor necrosis factor receptor superfamily, member 6b, decoy | 342852 | 466 | 342328 | 1631 | |
| AS | DcR3 | tumor necrosis factor receptor superfamily, member 6b, decoy | 369996 | 467 | 359013 | 1632 | |
| AS | DcR3 | tumor necrosis factor receptor superfamily, member 6b, decoy | 370006 | 468 | 359023 | 1633 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 338895 | 469 | 339524 | 1634 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 339350 | 470 | 343218 | 1635 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 341385 | 471 | 345906 | 1636 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 378206 | 472 | 367448 | 1637 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 378209 | 473 | 367454 | 1638 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 378212 | 474 | 367457 | 1639 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 430539 | 475 | 389502 | 1640 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 448632 | 476 | 411635 | 1641 | |
| AS | DFF40 (CAD) | DNA fragmentation factor, 40kDa, beta polypeptide (caspase-activated DNase) | 491998 | 477 | 436775 | 1642 | |
| AS | DR3 | tumor necrosis factor receptor superfamily, member 25 | 348333 | 478 | 314451 | 1643 | |
| AS | DR3 | tumor necrosis factor receptor superfamily, member 25 | 351748 | 479 | 326762 | 1644 | |
| AS | DR3 | tumor necrosis factor receptor superfamily, member 25 | 351959 | 480 | 337713 | 1645 | |
| AS | DR3 | tumor necrosis factor receptor superfamily, member 25 | 356876 | 481 | 349341 | 1646 | |
| AS | DR3 | tumor necrosis factor receptor superfamily, member 25 | 377782 | 482 | 367013 | 1647 | |
| AS | DR4 | tumor necrosis factor receptor | 221132 | 483 | 221132 | 1648 | |

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|---|---|---|---|---|---|---|---|
| | | superfamily, member 10a | | | | | |
| AS | DR5 | tumor necrosis factor receptor superfamily, member 10b | 276431 | 484 | 276431 | 1649 | |
| AS | DR5 | tumor necrosis factor receptor superfamily, member 10b | 347739 | 485 | 317859 | 1650 | |
| AS | DR5 | tumor necrosis factor receptor superfamily, member 10b | 542226 | 486 | 443386 | 1651 | |
| AS | DR6 | tumor necrosis factor receptor superfamily, member 21 | 296861 | 487 | 296861 | 1652 | |
| AS | DR6 | tumor necrosis factor receptor superfamily, member 21 | 419206 | 488 | 390032 | 1653 | |
| AS | EGFR | epidermal growth factor receptor | 275493 | 489 | 275493 | 1654 | |
| AS | EGFR | epidermal growth factor receptor | 342916 | 490 | 342376 | 1655 | |
| AS | EGFR | epidermal growth factor receptor | 344576 | 491 | 345973 | 1656 | |
| AS | EGFR | epidermal growth factor receptor | 395504 | 492 | 378880 | 1657 | |
| AS | EGFR | epidermal growth factor receptor | 420316 | 493 | 413843 | 1658 | |
| AS | EGFR | epidermal growth factor receptor | 442591 | 494 | 410031 | 1659 | |
| AS | EGFR | epidermal growth factor receptor | 454757 | 495 | 395243 | 1660 | |
| AS | EGFR | epidermal growth factor receptor | 455089 | 496 | 415559 | 1661 | |
| AS | EGFR | epidermal growth factor receptor | 533450 | 497 | 435262 | 1662 | |
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 269571 | 498 | 269571 | 1663 | |
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 406381 | 499 | 385185 | 1664 | |
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 445658 | 500 | 404047 | 1665 | |
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 540042 | 501 | 446382 | 1666 | |
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 540147 | 502 | 443562 | 1667 | |

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|---|---|---|---|---|---|---|---|
| AS | ErbB2 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | 541774 | 503 | 446466 | 1668 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 267101 | 504 | 267101 | 1669 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 394099 | 505 | 377659 | 1670 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 411731 | 506 | 415753 | 1671 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 415288 | 507 | 408340 | 1672 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 450146 | 508 | 399178 | 1673 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 549282 | 509 | 448636 | 1674 | |
| AS | ErbB3 | v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian) | 551085 | 510 | 448483 | 1675 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 1 | 215832 | 511 | 215832 | 1676 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 263025 | 512 | 263025 | 1677 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 322266 | 513 | 327293 | 1678 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 395200 | 514 | 378626 | 1679 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 395202 | 515 | 378628 | 1680 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 1 | 398822 | 516 | 381803 | 1681 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 403394 | 517 | 384895 | 1682 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 1 | 415911 | 518 | 409149 | 1683 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 3 | 484663 | 519 | 432742 | 1684 | |
| AS | Erk(MAPK1/3) | mitogen-activated protein kinase 1 | 544786 | 520 | 440842 | 1685 | |
| AS | FADD | Fas (TNFRSF6)-associated via death domain | 301838 | 521 | 301838 | 1686 | |
| AS | FLASH | caspase 8 associated protein 2 | 237177 | 522 | NA | 1687 | |
| AS | FLASH | caspase 8 associated protein 2 | 419040 | 523 | NA | | |
| AS | FLASH | caspase 8 associated protein 2 | 444163 | 524 | NA | | |
| AS | FLASH | caspase 8 associated protein 2 | 547893 | 525 | NA | | |
| AS | FLASH | caspase 8 associated protein 2 | 548224 | 526 | NA | | |

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|---|---|---|---|---|---|---|---|
| AS | FLASH | caspase 8 associated protein 2 | 551025 | 527 | NA | | |
| AS | FLASH | caspase 8 associated protein 2 | 552401 | 528 | NA | | |
| AS | FN14 | tumor necrosis factor receptor superfamily, member 12A | 326577 | 529 | 326737 | 1688 | |
| AS | FN14 | tumor necrosis factor receptor superfamily, member 12A | 341627 | 530 | 343894 | 1689 | |
| AS | GCK (MAP4 K2) | mitogen-activated protein kinase kinase kinase kinase 2 | 294066 | 531 | 294066 | 1690 | |
| AS | GRB2 | growth factor receptor-bound protein 2 | 316615 | 532 | 317360 | 1691 | |
| AS | GRB2 | growth factor receptor-bound protein 2 | 316804 | 533 | 339007 | 1692 | |
| AS | GRB2 | growth factor receptor-bound protein 2 | 392562 | 534 | 376345 | 1693 | |
| AS | GRB2 | growth factor receptor-bound protein 2 | 392564 | 535 | 376347 | 1694 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 311189 | 536 | 309845 | 1695 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 397594 | 537 | 380722 | 1696 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 397596 | 538 | 380723 | 1697 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 417302 | 539 | 388246 | 1698 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 451590 | 540 | 407586 | 1699 | |
| AS | H-Ras | v-Ha-ras Harvey rat sarcoma viral oncogene homolog | 493230 | 541 | 434023 | 1700 | |
| AS | HRK | harakiri, BCL2 interacting protein (contains only BH3 domain) | 257572 | 542 | 257572 | 1701 | |
| AS | HSP27 | heat shock 27kDa protein 1 | 248553 | 543 | 248553 | 1702 | |
| AS | HSP27 | heat shock 27kDa protein 3 | 302005 | 544 | 303394 | 1703 | |
| AS | HSP27 | Heat shock protein beta-2 | 304298 | 545 | 302476 | 1704 | |
| AS | HSP27 | heat shock 27kDa protein 1 | 432276 | 546 | 406545 | 1705 | |
| AS | HSP27 | Heat shock protein beta-2 | 537382 | 547 | 445585 | 1706 | |
| AS | HtrA2/Omi | HtrA serine peptidase 2 | 258080 | 548 | 258080 | 1707 | |
| AS | HtrA2/Omi | HtrA serine peptidase 2 | 352222 | 549 | 312893 | 1708 | |
| AS | Humanin | MT-RNR2-like 4 | 399974 | 550 | 382856 | 1709 | |
| AS | Humanin | MT-RNR2-like 5 | 512524 | 551 | 437910 | 1710 | |
| AS | Humanin | MT-RNR2-like 8 | 536684 | 552 | 439666 | 1711 | |
| AS | Humanin | MT-RNR2-like 1 | 540040 | 553 | 439228 | 1712 | |
| AS | Humanin | MT-RNR2-like 3 | 543500 | 554 | 443339 | 1713 | |
| AS | Humani | MT-RNR2-like 7 | 544824 | 555 | 439985 | 1714 | |

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| AS | Humani n | MT-RNR2-like 10 | 545075 | 556 | 442159 | 1715 | |
| AS | Humani n | MT-RNR2-like 6 | 570419 | 557 | 461075 | 1716 | |
| AS | ICAD | DNA fragmentation factor, 45kDa, alpha polypeptide | 377036 | 558 | 366235 | 1717 | |
| AS | ICAD | DNA fragmentation factor, 45kDa, alpha polypeptide | 377038 | 559 | 366237 | 1718 | |
| AS | IGF-1R | insulin-like growth factor 1 receptor | 268035 | 560 | 268035 | 1719 | |
| AS | IKK (alpha) | conserved helix-loop-helix ubiquitous kinase | 370397 | 561 | 359424 | 1720 | |
| AS | IKK (beta) | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta | 379708 | 562 | 369030 | 1721 | |
| AS | IKK (beta) | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta | 416505 | 563 | 404920 | 1722 | |
| AS | IKK (beta) | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta | 520810 | 564 | 430684 | 1723 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 263518 | 565 | 263518 | 1724 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 369601 | 566 | 358614 | 1725 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 369606 | 567 | 358619 | 1726 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 369607 | 568 | 358620 | 1727 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 369609 | 569 | 358622 | 1728 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 422680 | 570 | 390368 | 1729 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 440286 | 571 | 394934 | 1730 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 445622 | 572 | 395205 | 1731 | |
| AS | IKK-gamma | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma | 455588 | 573 | 400769 | 1732 | |
| AS | IRAK1 | interleukin-1 receptor-associated kinase 1 | 369980 | 574 | 358997 | 1733 | |
| AS | IRAK1 | interleukin-1 receptor-associated kinase 1 | 393682 | 575 | 377287 | 1734 | |
| AS | IRAK1 | interleukin-1 receptor-associated kinase 1 | 393687 | 576 | 377291 | 1735 | |

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|---|---|---|---|---|---|---|---|
| AS | IRAK1 | interleukin-1 receptor-associated kinase 1 | 429936 | 577 | 392662 | 1736 | |
| AS | IRAK2 | interleukin-1 receptor-associated kinase 2 | 256458 | 578 | 256458 | 1737 | |
| AS | IRS-1 | insulin receptor substrate 1 | 305123 | 579 | 304895 | 1738 | |
| AS | jBid; formed after cleaving BID at position 25 | jBID | NA | | NA | 1739 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 360332 | 580 | 353483 | 1740 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 374174 | 581 | 363289 | 1741 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 374176 | 582 | 363291 | 1742 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 374179 | 583 | 363294 | 1743 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 374182 | 584 | 363297 | 1744 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 374189 | 585 | 363304 | 1745 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 395611 | 586 | 378974 | 1746 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 426557 | 587 | 397729 | 1747 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 429041 | 588 | 393223 | 1748 | |
| AS | JNK1(MAPK8) | mitogen-activated protein kinase 8 | 432379 | 589 | 387936 | 1749 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 359221 | 590 | 352157 | 1750 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 361569 | 591 | 355297 | 1751 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 395157 | 592 | 378586 | 1752 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 395160 | 593 | 378589 | 1753 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 395161 | 594 | 378590 | 1754 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 395166 | 595 | 378595 | 1755 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 395169 | 596 | 378598 | 1756 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 449047 | 597 | 414469 | 1757 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 502302 | 598 | 423918 | 1758 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 503911 | 599 | 421409 | 1759 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 506773 | 600 | 421359 | 1760 | |

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|---|---|---|---|---|---|---|---|
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 509464 | 601 | 424128 | 1761 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 511167 | 602 | 422277 | 1762 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 511328 | 603 | 421762 | 1763 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 512017 | 604 | 424755 | 1764 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 512564 | 605 | 422985 | 1765 | |
| AS | JNK3(MAPK10) | mitogen-activated protein kinase 10 | 515400 | 606 | 424154 | 1766 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 169293 | 607 | 169293 | 1767 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 296280 | 608 | 296280 | 1768 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 337774 | 609 | 336792 | 1769 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 392472 | 610 | 376264 | 1770 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 541811 | 611 | 440446 | 1771 | |
| AS | MAP1 | mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor) | 541896 | 612 | 446240 | 1772 | |
| AS | Mcl-1 | myeloid cell leukemia sequence 1 (BCL2-related) | 307940 | 613 | 309973 | 1773 | |
| AS | Mcl-1 | myeloid cell leukemia sequence 1 (BCL2-related) | 369026 | 614 | 358022 | 1774 | |
| AS | Mcl-1 | myeloid cell leukemia sequence 1 (BCL2-related) | 439749 | 615 | 411395 | 1775 | |
| AS | MEK1(MAP2K1) | mitogen-activated protein kinase 1 | 215832 | 616 | 215832 | 1776 | |
| AS | MEK1(MAP2K1) | mitogen-activated protein kinase kinase 1 | 307102 | 617 | 302486 | 1777 | |
| AS | MEK1(MAP2K1) | mitogen-activated protein kinase 1 | 415911 | 618 | 409149 | 1778 | |
| AS | MEK1(MAP2K1) | mitogen-activated protein kinase 1 | 544786 | 619 | 440842 | 1779 | |
| AS | MEK2( | mitogen-activated protein | 262948 | 620 | 262948 | 1780 | |

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|---|---|---|---|---|---|---|---|
| | MAP2K 2) | kinase kinase 2 | | | | | |
| AS | MEK4 (MAP2 K4) | mitogen-activated protein kinase kinase 4 | 353533 | 621 | 262445 | 1781 | |
| AS | MEK4 (MAP2 K4) | mitogen-activated protein kinase kinase 4 | 415385 | 622 | 410402 | 1782 | |
| AS | MEK4 (MAP2 K4) | mitogen-activated protein kinase kinase 4 | 536413 | 623 | 441610 | 1783 | |
| AS | MEK4 (MAP2 K4) | mitogen-activated protein kinase kinase 4 | 538465 | 624 | 444874 | 1784 | |
| AS | MEKK1 (MAP3 K1) | mitogen-activated protein kinase kinase kinase 1 | 399503 | 625 | 382423 | 1785 | |
| AS | NADE (NGFR AP1) | nerve growth factor receptor (TNFRSF16) associated protein 1 | 299872 | 626 | 299872 | 1786 | |
| AS | NADE (NGFR AP1) | nerve growth factor receptor (TNFRSF16) associated protein 1 | 361298 | 627 | 354843 | 1787 | |
| AS | NADE (NGFR AP1) | nerve growth factor receptor (TNFRSF16) associated protein 1 | 372634 | 628 | 361717 | 1788 | |
| AS | NADE (NGFR AP1) | nerve growth factor receptor (TNFRSF16) associated protein 1 | 372635 | 629 | 361718 | 1789 | |
| AS | NADE (NGFR AP1) | nerve growth factor receptor (TNFRSF16) associated protein 1 | 372645 | 630 | 361728 | 1790 | |
| AS | NGF | nerve growth factor (beta polypeptide) | 369512 | 631 | 358525 | 1791 | |
| AS | NGFR | nerve growth factor receptor | 172229 | 632 | 172229 | 1792 | |
| AS | NGFR | nerve growth factor receptor | 504201 | 633 | 421731 | 1793 | |
| AS | NIK (MAP3 K14) | mitogen-activated protein kinase kinase kinase 14 | 344686 | 634 | 342059 | 1794 | |
| AS | NIK (MAP3 K14) | mitogen-activated protein kinase kinase kinase 14 | 376926 | 635 | 366125 | 1795 | |
| AS | NOXA | phorbol-12-myristate-13-acetate-induced protein 1 | 269518 | 636 | 269518 | 1796 | |
| AS | NOXA | phorbol-12-myristate-13-acetate-induced protein 1 | 316660 | 637 | 326119 | 1797 | |
| AS | OX40 | tumor necrosis factor receptor superfamily, member 4 | 379236 | 638 | 368538 | 1798 | |
| AS | OX40 | tumor necrosis factor receptor superfamily, member 4 | 453580 | 639 | 390907 | 1799 | |
| AS | OX40L( TNFSF4 ) | tumor necrosis factor (ligand) superfamily, member 4 | 281834 | 640 | 281834 | 1800 | |
| AS | OX40L( | tumor necrosis factor (ligand) | 367718 | 641 | 356691 | 1801 | |

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|---|---|---|---|---|---|---|---|
| | TNFSF4 ) | superfamily, member 4 | | | | | |
| AS | OX40L( TNFSF4 ) | tumor necrosis factor (ligand) superfamily, member 4 | 545292 | 642 | 439704 | 1802 | |
| AS | p53 | tumor protein p53 | 269305 | 643 | 269305 | 1803 | |
| AS | p53 | tumor protein p53 | 269305 | 644 | 269305 | 1804 | 2489 |
| AS | p53 | tumor protein p53 | 359597 | 645 | 352610 | 1805 | |
| AS | p53 | tumor protein p53 | 396473 | 646 | 379735 | 1806 | |
| AS | p53 | tumor protein p53 | 413465 | 647 | 410739 | 1807 | |
| AS | p53 | tumor protein p53 | 414315 | 648 | 394195 | 1808 | |
| AS | p53 | tumor protein p53 | 419024 | 649 | 402130 | 1809 | |
| AS | p53 | tumor protein p53 | 420246 | 650 | 391127 | 1810 | |
| AS | p53 | tumor protein p53 | 445888 | 651 | 391478 | 1811 | 2490 |
| AS | p53 | tumor protein p53 | 455263 | 652 | 398846 | 1812 | |
| AS | p53 | tumor protein p53 | 503591 | 653 | 426252 | 1813 | |
| AS | p53 | tumor protein p53 | 508793 | 654 | 424104 | 1814 | |
| AS | p53 | tumor protein p53 | 509690 | 655 | 425104 | 1815 | |
| AS | p53 | tumor protein p53 | 514944 | 656 | 423862 | 1816 | |
| AS | p53 | tumor protein p53 | 545858 | 657 | 437792 | 1817 | |
| AS | p70 S6 kinase 1 | ribosomal protein S6 kinase, 70kDa, polypeptide 1 | 225577 | 658 | 225577 | 1818 | |
| AS | p70 S6 kinase 1 | ribosomal protein S6 kinase, 70kDa, polypeptide 1 | 393021 | 659 | 376744 | 1819 | |
| AS | p70 S6 kinase 1 | ribosomal protein S6 kinase, 70kDa, polypeptide 1 | 406116 | 660 | 384335 | 1820 | |
| AS | p70 S6 kinase 1 | ribosomal protein S6 kinase, 70kDa, polypeptide 1 | 443572 | 661 | 441993 | 1821 | |
| AS | p70 S6 kinase 2 | ribosomal protein S6 kinase, 70kDa, polypeptide 2 | 312629 | 662 | 308413 | 1822 | |
| AS | p70 S6 kinase 2 | ribosomal protein S6 kinase, 70kDa, polypeptide 2 | 528964 | 663 | 432847 | 1823 | |
| AS | p70 S6 kinase 2 | ribosomal protein S6 kinase, 70kDa, polypeptide 2 | 539188 | 664 | 442949 | 1824 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 374162 | 665 | 363277 | 1825 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 374164 | 666 | 363279 | 1826 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 374168 | 667 | 363283 | 1827 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 403732 | 668 | 383967 | 1828 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 530003 | 669 | 432281 | 1829 | |
| AS | p90Rsk | ribosomal protein S6 kinase, 90kDa, polypeptide 1 | 531382 | 670 | 435412 | 1830 | |
| AS | PAK2 | p21 protein (Cdc42/Rac)-activated kinase 2 | 327134 | 671 | 314067 | 1831 | |
| AS | PARP-1 | poly (ADP-ribose) polymerase 1 | 366790 | 672 | 355755 | 1832 | |

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|---|---|---|---|---|---|---|---|
| AS | PARP-1 | poly (ADP-ribose) polymerase 1 | 366791 | 673 | 355756 | 1833 | |
| AS | PARP-1 | poly (ADP-ribose) polymerase 1 | 366792 | 674 | 355757 | 1834 | |
| AS | PARP-1 | poly (ADP-ribose) polymerase 1 | 366794 | 675 | 355759 | 1835 | |
| AS | PARP-1 | poly (ADP-ribose) polymerase 1 | 432338 | 676 | 412774 | 1836 | |
| AS | PDPK1 | 3-phosphoinositide dependent protein kinase-1 | 342085 | 677 | 344220 | 1837 | |
| AS | PDPK1 | 3-phosphoinositide dependent protein kinase-1 | 354836 | 678 | 346895 | 1838 | |
| AS | PDPK1 | 3-phosphoinositide dependent protein kinase-1 | 441549 | 679 | 395357 | 1839 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, alpha polypeptide | 263967 | 680 | 263967 | 1840 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 289153 | 681 | 289153 | 1841 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, gamma polypeptide | 359195 | 682 | 352121 | 1842 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, delta polypeptide | 360563 | 683 | 353766 | 1843 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, delta polypeptide | 361110 | 684 | 354410 | 1844 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, delta polypeptide | 377346 | 685 | 366563 | 1845 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, gamma polypeptide | 440650 | 686 | 392258 | 1846 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 461451 | 687 | 420399 | 1847 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, alpha polypeptide | 468036 | 688 | 417479 | 1848 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 477593 | 689 | 418143 | 1849 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 483968 | 690 | 419857 | 1850 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 493568 | 691 | 417869 | 1851 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, gamma polypeptide | 496166 | 692 | 419260 | 1852 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, delta polypeptide | 536656 | 693 | 446444 | 1853 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, delta polypeptide | 543390 | 694 | 443811 | 1854 | |
| AS | PI3K | phosphoinositide-3-kinase, catalytic, beta polypeptide | 544716 | 695 | 438259 | 1855 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, alpha | 308677 | 696 | 309591 | 1856 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, alpha | 350356 | 697 | 340940 | 1857 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370679 | 698 | 359713 | 1858 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370680 | 699 | 359714 | 1859 | |

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|---|---|---|---|---|---|---|---|
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370681 | 700 | 359715 | 1860 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370682 | 701 | 359716 | 1861 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370684 | 702 | 359718 | 1862 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370685 | 703 | 359719 | 1863 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370688 | 704 | 359722 | 1864 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 370689 | 705 | 359723 | 1865 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, gamma | 377276 | 706 | 366488 | 1866 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 394838 | 707 | 378314 | 1867 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 394839 | 708 | 378315 | 1868 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 413538 | 709 | 397175 | 1869 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 417530 | 710 | 399326 | 1870 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 432111 | 711 | 392275 | 1871 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 436133 | 712 | 390906 | 1872 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 446538 | 713 | 401252 | 1873 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, beta | 450730 | 714 | 393654 | 1874 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, alpha | 535695 | 715 | 441654 | 1875 | |
| AS | PKA-cat | protein kinase, cAMP-dependent, catalytic, alpha | 536649 | 716 | 440418 | 1876 | |
| AS | PKC-delta | protein kinase C, delta | 330452 | 717 | 331602 | 1877 | |
| AS | PKC-delta | protein kinase C, delta | 394729 | 718 | 378217 | 1878 | |
| AS | PKC-delta | protein kinase C, delta | 478843 | 719 | 419726 | 1879 | |
| AS | PKC-delta | protein kinase C, delta | 487897 | 720 | 418106 | 1880 | |
| AS | PKC-Zeta | protein kinase C, zeta | 378567 | 721 | 367830 | 1881 | |
| AS | PKC-Zeta | protein kinase C, zeta | 400920 | 722 | 383711 | 1882 | |
| AS | PKC-Zeta | protein kinase C, zeta | 400921 | 723 | 383712 | 1883 | |
| AS | PKC-Zeta | protein kinase C, zeta | 461106 | 724 | 426412 | 1884 | |
| AS | PKC-Zeta | protein kinase C, zeta | 470511 | 725 | 421350 | 1885 | |
| AS | PKC-Zeta | protein kinase C, zeta | 470596 | 726 | 424228 | 1886 | |

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|---|---|---|---|---|---|---|---|
| AS | PKC-Zeta | protein kinase C, zeta | 470986 | 727 | 421219 | 1887 | |
| AS | PKC-Zeta | protein kinase C, zeta | 482686 | 728 | 425317 | 1888 | |
| AS | PKC-Zeta | protein kinase C, zeta | 496325 | 729 | 421869 | 1889 | |
| AS | PP1-cat alpha | protein phosphatase 1, catalytic subunit, alpha isozyme | 312989 | 730 | 326031 | 1890 | |
| AS | PP1-cat alpha | protein phosphatase 1, catalytic subunit, alpha isozyme | 376745 | 731 | 365936 | 1891 | |
| AS | PP1-cat alpha | protein phosphatase 1, catalytic subunit, alpha isozyme | 451458 | 732 | 405603 | 1892 | |
| AS | PP2a catalytic | protein phosphatase 2, catalytic subunit, alpha isozyme | 481195 | 733 | 418447 | 1893 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1H | 228705 | 734 | 228705 | 1894 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1F | 263212 | 735 | 263212 | 1895 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 282412 | 736 | 282412 | 1896 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1K | 295908 | 737 | 295908 | 1897 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1M | 296487 | 738 | 296487 | 1898 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1D | 305921 | 739 | 306682 | 1899 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1E | 308249 | 740 | 312411 | 1900 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1J | 309276 | 741 | 308926 | 1901 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1K | 315194 | 742 | 324761 | 1902 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1M | 323588 | 743 | 319894 | 1903 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1N (putative) | 324688 | 744 | 321761 | 1904 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 325642 | 745 | 327255 | 1905 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 325658 | 746 | 314850 | 1906 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1G | 344034 | 747 | 342778 | 1907 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 345249 | 748 | 326089 | 1908 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1G | 350803 | 749 | 264714 | 1909 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1J | 359994 | 750 | 353088 | 1910 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 378551 | 751 | 367813 | 1911 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1D | 392995 | 752 | 376720 | 1912 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 395076 | 753 | 378514 | 1913 | |

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|---|---|---|---|---|---|---|---|
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1G | 395543 | 754 | 378913 | 1914 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1N (putative) | 396734 | 755 | 379960 | 1915 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1F | 397495 | 756 | 380632 | 1916 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1F | 406981 | 757 | 384715 | 1917 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1F | 407142 | 758 | 384930 | 1918 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 409432 | 759 | 387287 | 1919 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1M | 409502 | 760 | 387046 | 1920 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 409895 | 761 | 387341 | 1921 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1B | 419807 | 762 | 390087 | 1922 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1E | 443121 | 763 | 390257 | 1923 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1M | 457351 | 764 | 393747 | 1924 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1L | 497343 | 765 | 420354 | 1925 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1L | 498165 | 766 | 417659 | 1926 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1K | 506423 | 767 | 424155 | 1927 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 525399 | 768 | 435398 | 1928 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 528241 | 769 | 431453 | 1929 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 529574 | 770 | 432966 | 1930 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1A | 531937 | 771 | 435575 | 1931 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1F | 538191 | 772 | 439915 | 1932 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1G | 544412 | 773 | 442536 | 1933 | |
| AS | PP2C | protein phosphatase, Mg2+/Mn2+ dependent, 1D | 544712 | 774 | 438518 | 1934 | |
| AS | Puma | BCL2 binding component 3 | 300880 | 775 | 300880 | 1935 | |
| AS | Puma | BCL2 binding component 3 | 341983 | 776 | 341155 | 1936 | |
| AS | Puma | BCL2 binding component 3 | 439096 | 777 | 395862 | 1937 | |
| AS | Puma | BCL2 binding component 3 | 449228 | 778 | 404503 | 1938 | |
| AS | RAIDD | CASP2 and RIPK1 domain containing adaptor with death domain | 332896 | 779 | 327647 | 1939 | |
| AS | RAIDD | CASP2 and RIPK1 domain containing adaptor with death domain | 541813 | 780 | 442624 | 1940 | |

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|---|---|---|---|---|---|---|---|
| AS | RAIDD | CASP2 and RIPK1 domain containing adaptor with death domain | 542893 | 781 | 439068 | 1941 | |
| AS | RAIDD | CASP2 and RIPK1 domain containing adaptor with death domain | 551065 | 782 | 448425 | 1942 | |
| AS | RANK | tumor necrosis factor receptor superfamily, member 11a, NFKB activator | 269485 | 783 | 269485 | 1943 | |
| AS | RANK | tumor necrosis factor receptor superfamily, member 11a, NFKB activator | 382790 | 784 | 372240 | 1944 | |
| AS | RANKL | tumor necrosis factor (ligand) superfamily, member 11 | 239849 | 785 | 239849 | 1945 | |
| AS | RANKL | tumor necrosis factor (ligand) superfamily, member 11 | 358545 | 786 | 351347 | 1946 | |
| AS | RANKL | tumor necrosis factor (ligand) superfamily, member 11 | 398795 | 787 | 381775 | 1947 | |
| AS | RANKL | tumor necrosis factor (ligand) superfamily, member 11 | 405262 | 788 | 384042 | 1948 | |
| AS | RANKL | tumor necrosis factor (ligand) superfamily, member 11 | 544862 | 789 | 444913 | 1949 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 308639 | 790 | 311508 | 1950 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 406246 | 791 | 384273 | 1951 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 426617 | 792 | 437980 | 1952 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 525693 | 793 | 432537 | 1953 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 526283 | 794 | 435290 | 1954 | |
| AS | ReIA (p65 NF-kappaB subunit) | v-rel reticuloendotheliosis viral oncogene homolog A (avian) | 545816 | 795 | 443700 | 1955 | |
| AS | RIPK1 | receptor (TNFRSF)-interacting serine-threonine kinase 1 | 259808 | 796 | 259808 | 1956 | |
| AS | RIPK1 | receptor (TNFRSF)-interacting | 380409 | 797 | 369773 | 1957 | |

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|---|---|---|---|---|---|---|---|
| | | serine-threonine kinase 1 | | | | | |
| AS | RIPK1 | receptor (TNFRSF)-interacting serine-threonine kinase 1 | 453483 | 798 | 415981 | 1958 | |
| AS | RIPK1 | receptor (TNFRSF)-interacting serine-threonine kinase 1 | 541791 | 799 | 442294 | 1959 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 360718 | 800 | 353944 | 1960 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 376929 | 801 | 366128 | 1961 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 389805 | 802 | 374455 | 1962 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 402874 | 803 | 385553 | 1963 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 422245 | 804 | 394534 | 1964 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 454378 | 805 | 408107 | 1965 | |
| AS | Sequestosome 1 (p62) | sequestosome 1 | 514093 | 806 | 427308 | 1966 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 2 | 264554 | 807 | 264554 | 1967 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 366442 | 808 | 396162 | 1968 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368441 | 809 | 357426 | 1969 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368443 | 810 | 357428 | 1970 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368445 | 811 | 357430 | 1971 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368449 | 812 | 357434 | 1972 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368450 | 813 | 357435 | 1973 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 368453 | 814 | 357438 | 1974 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 3 | 375830 | 815 | 364990 | 1975 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming | 375831 | 816 | 364991 | 1976 | |

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|---|---|---|---|---|---|---|---|
| | | protein 3 | | | | | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 3 | 375835 | 817 | 364995 | 1977 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 412170 | 818 | 398441 | 1978 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 414115 | 819 | 404908 | 1979 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 444179 | 820 | 398864 | 1980 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 444664 | 821 | 396333 | 1981 | |
| AS | Shc | SHC (Src homology 2 domain containing) transforming protein 1 | 448116 | 822 | 401303 | 1982 | |
| AS | Siah-1 | seven in absentia homolog 1 (Drosophila) | 356721 | 823 | 349156 | 1983 | |
| AS | Siah-1 | seven in absentia homolog 1 (Drosophila) | 380006 | 824 | 369343 | 1984 | |
| AS | Siah-1 | seven in absentia homolog 1 (Drosophila) | 394725 | 825 | 378214 | 1985 | |
| AS | SMAC | diablo, IAP-binding mitochondrial protein | NA | 826 | NA | 1986 | |
| AS | Smac/Diablo | diablo, IAP-binding mitochondrial protein | 267169 | 827 | 267169 | 1987 | |
| AS | Smac/Diablo | diablo, IAP-binding mitochondrial protein | 353548 | 828 | 320343 | 1988 | |
| AS | Smac/Diablo | diablo, IAP-binding mitochondrial protein | 413918 | 829 | 411638 | 1989 | |
| AS | Smac/Diablo | diablo, IAP-binding mitochondrial protein | 443649 | 830 | 398495 | 1990 | |
| AS | Smac/Diablo | diablo, IAP-binding mitochondrial protein | 464942 | 831 | 442360 | 1991 | |
| AS | SODD | BCL2-associated athanogene 4 | 287322 | 832 | 287322 | 1992 | |
| AS | SODD | BCL2-associated athanogene 4 | 432471 | 833 | 393298 | 1993 | |
| AS | SOS | son of sevenless homolog 2 (Drosophila) | 216373 | 834 | 216373 | 1994 | |
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 263879 | 835 | 263879 | 1995 | |
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 395038 | 836 | 378479 | 1996 | |
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 402219 | 837 | 384675 | 1997 | |
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 426016 | 838 | 387784 | 1998 | |
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 428721 | 839 | 399992 | 1999 | |
| AS | SOS | son of sevenless homolog 2 (Drosophila) | 543680 | 840 | 445328 | 2000 | |

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|---|---|---|---|---|---|---|---|
| AS | SOS | son of sevenless homolog 1 (Drosophila) | 543698 | 841 | 441172 | 2001 | |
| AS | SUMO-1 | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae) | 392244 | 842 | 376075 | 2002 | |
| AS | SUMO-1 | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae) | 392245 | 843 | 376076 | 2003 | |
| AS | SUMO-1 | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae) | 392246 | 844 | 376077 | 2004 | |
| AS | SUMO-1 | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae) | 409205 | 845 | 386267 | 2005 | |
| AS | SUMO-1 | SMT3 suppressor of mif two 3 homolog 1 (S. cerevisiae) | 409498 | 846 | 386472 | 2006 | |
| AS | Survivin | baculoviral IAP repeat containing 5 | 301633 | 847 | 301633 | 2007 | |
| AS | Survivin | baculoviral IAP repeat containing 5 | 350051 | 848 | 324180 | 2008 | |
| AS | Survivin | baculoviral IAP repeat containing 5 | 374948 | 849 | 364086 | 2009 | |
| AS | Survivin | baculoviral IAP repeat containing 5 | 432014 | 850 | 389088 | 2010 | |
| AS | TACI | tumor necrosis factor receptor superfamily, member 13B | 261652 | 851 | 261652 | 2011 | |
| AS | TACI | tumor necrosis factor receptor superfamily, member 13B | 437538 | 852 | 413453 | 2012 | |
| AS | tBid | tBID | NA | | NA | 2013 | |
| AS | TL1A | tumor necrosis factor (ligand) superfamily, member 15 | 374044 | 853 | 363156 | 2014 | |
| AS | TL1A | tumor necrosis factor (ligand) superfamily, member 15 | 374045 | 854 | 363157 | 2015 | |
| AS | TNF-alpha | tumor necrosis factor | 376122 | 855 | 365290 | 2016 | |
| AS | TNF-alpha | tumor necrosis factor | 383496 | 856 | 372988 | 2017 | |
| AS | TNF-alpha | tumor necrosis factor | 412275 | 857 | 392858 | 2018 | |
| AS | TNF-alpha | tumor necrosis factor | 420425 | 858 | 410668 | 2019 | |
| AS | TNF-alpha | tumor necrosis factor | 443707 | 859 | 389492 | 2020 | |
| AS | TNF-alpha | tumor necrosis factor | 445232 | 860 | 389265 | 2021 | |
| AS | TNF-alpha | tumor necrosis factor | 448781 | 861 | 389490 | 2022 | |
| AS | TNF-alpha | tumor necrosis factor | 449264 | 862 | 398698 | 2023 | |
| AS | TNF-R1 | tumor necrosis factor receptor superfamily, member 1A | 162749 | 863 | 162749 | 2024 | |
| AS | TNF-R1 | tumor necrosis factor receptor superfamily, member 1A | 366159 | 864 | 380389 | 2025 | |
| AS | TNF-R2 | tumor necrosis factor receptor superfamily, member 1B | 376259 | 865 | 365435 | 2026 | |
| AS | TNF-R2 | tumor necrosis factor receptor superfamily, member 1B | 376259 | 866 | 365435 | 2027 | 2491 |
| AS | TNF-R2 | tumor necrosis factor receptor | 400863 | 867 | 383660 | 2028 | |

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| | | superfamily, member 1B | | | | | |
| AS | TNF-R2 | tumor necrosis factor receptor superfamily, member 1B | 536782 | 868 | 440425 | 2029 | |
| AS | TRADD | TNFRSF1A-associated via death domain | 345057 | 869 | 341268 | 2030 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 247668 | 870 | 247668 | 2031 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 359662 | 871 | 352685 | 2032 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 371645 | 872 | 360708 | 2033 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 414589 | 873 | 397653 | 2034 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 419057 | 874 | 405860 | 2035 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 429509 | 875 | 406524 | 2036 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 432785 | 876 | 400061 | 2037 | |
| AS | TRAF2 | TNF receptor-associated factor 2 | 536468 | 877 | 446414 | 2038 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 347662 | 878 | 328003 | 2039 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 351691 | 879 | 332468 | 2040 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 392745 | 880 | 376500 | 2041 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 539721 | 881 | 445998 | 2042 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 560371 | 882 | 454207 | 2043 | |
| AS | TRAF3 | TNF receptor-associated factor 3 | 560463 | 883 | 453623 | 2044 | |
| AS | TRAF5 | TNF receptor-associated factor 5 | 261464 | 884 | 261464 | 2045 | |
| AS | TRAF5 | TNF receptor-associated factor 5 | 336184 | 885 | 336825 | 2046 | |
| AS | TRAF5 | TNF receptor-associated factor 5 | 367004 | 886 | 355971 | 2047 | |
| AS | TRAF5 | TNF receptor-associated factor 5 | 427925 | 887 | 389891 | 2048 | |
| AS | TRAF6 | TNF receptor-associated factor 6 | 348124 | 888 | 337853 | 2049 | |
| AS | TRAF6 | TNF receptor-associated factor 6 | 526995 | 889 | 433623 | 2050 | |
| AS | TrkA | neurotrophic tyrosine kinase, receptor, type 1 | 368196 | 890 | 357179 | 2051 | |
| AS | TrkA | neurotrophic tyrosine kinase, receptor, type 1 | 392302 | 891 | 376120 | 2052 | |
| AS | TrkA | neurotrophic tyrosine kinase, receptor, type 1 | 524377 | 892 | 431418 | 2053 | |
| AS | TWEAK (TNFSF 12) | tumor necrosis factor (ligand) superfamily, member 12 | 293825 | 893 | 293825 | 2054 | |

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|---|---|---|---|---|---|---|---|
| AS | TWEAK (TNFSF 12) | tumor necrosis factor (ligand) superfamily, member 12 | 557233 | 894 | 451451 | 2055 | |
| AS | VDAC 1 | voltage-dependent anion channel 1 | 265333 | 895 | 265333 | 2056 | |
| AS | VDAC 1 | voltage-dependent anion channel 1 | 395044 | 896 | 378484 | 2057 | |
| AS | VDAC 1 | voltage-dependent anion channel 1 | 395047 | 897 | 378487 | 2058 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 298468 | 898 | 298468 | 2059 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 313132 | 899 | 361635 | 2060 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 332211 | 900 | 361686 | 2061 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 344036 | 901 | 344876 | 2062 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 413289 | 902 | 389551 | 2063 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 447677 | 903 | 401492 | 2064 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 535553 | 904 | 445901 | 2065 | |
| AS | VDAC 2 | voltage-dependent anion channel 2 | 543351 | 905 | 443092 | 2066 | |
| AS | XIAP | X-linked inhibitor of apoptosis | 355640 | 906 | 347858 | 2067 | |
| AS | XIAP | X-linked inhibitor of apoptosis | 371199 | 907 | 360242 | 2068 | |
| AS | XIAP | X-linked inhibitor of apoptosis | 430625 | 908 | 400637 | 2069 | |
| AS | XIAP | X-linked inhibitor of apoptosis | 434753 | 909 | 395230 | 2070 | |
| AS | XIAP | X-linked inhibitor of apoptosis | NA | 910 | NA | 2071 | |
| CC/S | ATM | ataxia telangiectasia mutated | 278616 | 911 | 278616 | 2072 | |
| CC/S | ATM | ataxia telangiectasia mutated | 389511 | 912 | 374162 | 2073 | |
| CC/S | ATM | ataxia telangiectasia mutated | 452508 | 913 | 388058 | 2074 | |
| CC/S | ATM | ataxia telangiectasia mutated | 532931 | 914 | 432318 | 2075 | |
| CC/S | ATR | ataxia telangiectasia and Rad3 related | 350721 | 915 | 343741 | 2076 | |
| CC/S | ATR | ataxia telangiectasia and Rad3 related | 383101 | 916 | 372581 | 2077 | |
| CC/S | ATRIP | ATR interacting protein | 320211 | 917 | 323099 | 2078 | |
| CC/S | ATRIP | ATR interacting protein | 346691 | 918 | 302338 | 2079 | |
| CC/S | ATRIP | ATR interacting protein | 357105 | 919 | 349620 | 2080 | |
| CC/S | ATRIP | ATR interacting protein | 412052 | 920 | 400930 | 2081 | |
| CC/S | ATRIP | ATR interacting protein | 421175 | 921 | 406664 | 2082 | |
| CC/S | Bard1 | BRCA1 associated RING domain 1 | 260947 | 922 | 260947 | 2083 | |
| CC/S | Bard1 | BRCA1 associated RING domain 1 | 449967 | 923 | 406752 | 2084 | |
| CC/S | BLM | Bloom syndrome, RecQ helicase-like | 355112 | 924 | 347232 | 2085 | |
| CC/S | BLM | Bloom syndrome, RecQ | 536925 | 925 | 442330 | 2086 | |

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|---|---|---|---|---|---|---|---|
| | | helicase-like | | | | | |
| CC/S | BLM | Bloom syndrome, RecQ helicase-like | 543977 | 926 | 439075 | 2087 | |
| CC/S | Brca1 | breast cancer 1, early onset | 309486 | 927 | 310938 | 2088 | |
| CC/S | Brca1 | breast cancer 1, early onset | 346315 | 928 | 246907 | 2089 | |
| CC/S | Brca1 | breast cancer 1, early onset | 351666 | 929 | 338007 | 2090 | |
| CC/S | Brca1 | breast cancer 1, early onset | 352993 | 930 | 312236 | 2091 | |
| CC/S | Brca1 | breast cancer 1, early onset | 354071 | 931 | 326002 | 2092 | |
| CC/S | Brca1 | breast cancer 1, early onset | 357654 | 932 | 350283 | 2093 | |
| CC/S | Brca1 | breast cancer 1, early onset | 393691 | 933 | 377294 | 2094 | |
| CC/S | Brca1 | breast cancer 1, early onset | 412061 | 934 | 397145 | 2095 | |
| CC/S | Brca1 | breast cancer 1, early onset | 461221 | 935 | 418548 | 2096 | |
| CC/S | Brca1 | breast cancer 1, early onset | 461798 | 936 | 417988 | 2097 | |
| CC/S | Brca1 | breast cancer 1, early onset | 468300 | 937 | 417148 | 2098 | |
| CC/S | Brca1 | breast cancer 1, early onset | 470026 | 938 | 419274 | 2099 | |
| CC/S | Brca1 | breast cancer 1, early onset | 471181 | 939 | 418960 | 2100 | |
| CC/S | Brca1 | breast cancer 1, early onset | 476777 | 940 | 417554 | 2101 | |
| CC/S | Brca1 | breast cancer 1, early onset | 477152 | 941 | 419988 | 2102 | |
| CC/S | Brca1 | breast cancer 1, early onset | 478531 | 942 | 420412 | 2103 | |
| CC/S | Brca1 | breast cancer 1, early onset | 484087 | 943 | 419481 | 2104 | |
| CC/S | Brca1 | breast cancer 1, early onset | 489037 | 944 | 420781 | 2105 | |
| CC/S | Brca1 | breast cancer 1, early onset | 491747 | 945 | 420705 | 2106 | |
| CC/S | Brca1 | breast cancer 1, early onset | 492859 | 946 | 420253 | 2107 | |
| CC/S | Brca1 | breast cancer 1, early onset | 493795 | 947 | 418775 | 2108 | |
| CC/S | Brca1 | breast cancer 1, early onset | 493919 | 948 | 418819 | 2109 | |
| CC/S | Brca1 | breast cancer 1, early onset | 494123 | 949 | 419103 | 2110 | |
| CC/S | Brca1 | breast cancer 1, early onset | 497488 | 950 | 418986 | 2111 | |
| CC/S | c-Abl | c-abl oncogene 1, non-receptor tyrosine kinase | 318560 | 951 | 323315 | 2112 | |
| CC/S | c-Abl | c-abl oncogene 1, non-receptor tyrosine kinase | 372348 | 952 | 361423 | 2113 | |
| CC/S | c-Abl | c-abl oncogene 1, non-receptor tyrosine kinase | 393293 | 953 | 376971 | 2114 | |
| CC/S | c-Abl | c-abl oncogene 1, non-receptor tyrosine kinase | 438426 | 954 | 407756 | 2115 | |
| CC/S | c-Abl | c-abl oncogene 1, non-receptor tyrosine kinase | 444970 | 955 | 400412 | 2116 | |
| CC/S | CDC25 A | cell division cycle 25 homolog A (S. pombe) | 302506 | 956 | 303706 | 2117 | |
| CC/S | CDC25 A | cell division cycle 25 homolog A (S. pombe) | 351231 | 957 | 343166 | 2118 | |
| CC/S | CDC25 A | cell division cycle 25 homolog A (S. pombe) | 437972 | 958 | 404285 | 2119 | |
| CC/S | CDC25 B | cell division cycle 25 homolog B (S. pombe) | 245960 | 959 | 245960 | 2120 | |
| CC/S | CDC25 B | cell division cycle 25 homolog B (S. pombe) | 340833 | 960 | 339170 | 2121 | |

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|---|---|---|---|---|---|---|---|
| CC/S | CDC25 B | cell division cycle 25 homolog B (S. pombe) | 344256 | 961 | 339125 | 2122 | |
| CC/S | CDC25 B | cell division cycle 25 homolog B (S. pombe) | 379598 | 962 | 368918 | 2123 | |
| CC/S | CDC25 B | cell division cycle 25 homolog B (S. pombe) | 439880 | 963 | 405972 | 2124 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 323760 | 964 | 321656 | 2125 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 348983 | 965 | 345205 | 2126 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 356505 | 966 | 348898 | 2127 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 357274 | 967 | 349821 | 2128 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 415130 | 968 | 392631 | 2129 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 503022 | 969 | 427251 | 2130 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 513970 | 970 | 424795 | 2131 | |
| CC/S | CDC25 C | cell division cycle 25 homolog C (S. pombe) | 534892 | 971 | 443196 | 2132 | |
| CC/S | CDK2 | cyclin-dependent kinase 2 | 266970 | 972 | 266970 | 2133 | |
| CC/S | CDK2 | cyclin-dependent kinase 2 | 354056 | 973 | 243067 | 2134 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 257904 | 974 | 257904 | 2135 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 312990 | 975 | 316889 | 2136 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 540325 | 976 | 439076 | 2137 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 552254 | 977 | 449179 | 2138 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 552388 | 978 | 448963 | 2139 | |
| CC/S | CDK4 | cyclin-dependent kinase 4 | 552862 | 979 | 446763 | 2140 | |
| CC/S | CDK6 | cyclin-dependent kinase 6 | 265734 | 980 | 265734 | 2141 | |
| CC/S | CDK6 | cyclin-dependent kinase 6 | 424848 | 981 | 397087 | 2142 | |
| CC/S | Chk1 | checkpoint kinase 1 | 278916 | 982 | 278916 | 2143 | |
| CC/S | Chk1 | checkpoint kinase 1 | 428830 | 983 | 412504 | 2144 | |
| CC/S | Chk1 | checkpoint kinase 1 | 438015 | 984 | 388648 | 2145 | |
| CC/S | Chk1 | checkpoint kinase 1 | 524737 | 985 | 432890 | 2146 | |
| CC/S | Chk1 | checkpoint kinase 1 | 525396 | 986 | 434141 | 2147 | |
| CC/S | Chk1 | checkpoint kinase 1 | 526937 | 987 | 431815 | 2148 | |
| CC/S | Chk1 | checkpoint kinase 1 | 527013 | 988 | 431525 | 2149 | |
| CC/S | Chk1 | checkpoint kinase 1 | 534070 | 989 | 435371 | 2150 | |
| CC/S | Chk1 | checkpoint kinase 1 | 534685 | 990 | 432470 | 2151 | |
| CC/S | Chk1 | checkpoint kinase 1 | 544373 | 991 | 442317 | 2152 | |
| CC/S | Chk2 | checkpoint kinase 2 | 328354 | 992 | 329178 | 2153 | |
| CC/S | Chk2 | checkpoint kinase 2 | 348295 | 993 | 329012 | 2154 | |
| CC/S | Chk2 | checkpoint kinase 2 | 382563 | 994 | 372003 | 2155 | |
| CC/S | Chk2 | checkpoint kinase 2 | 382565 | 995 | 372006 | 2156 | |
| CC/S | Chk2 | checkpoint kinase 2 | 382566 | 996 | 372007 | 2157 | |

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|---|---|---|---|---|---|---|---|
| CC/S | Chk2 | checkpoint kinase 2 | 382578 | 997 | 372021 | 2158 | |
| CC/S | Chk2 | checkpoint kinase 2 | 382580 | 998 | 372023 | 2159 | |
| CC/S | Chk2 | checkpoint kinase 2 | 402731 | 999 | 384835 | 2160 | |
| CC/S | Chk2 | checkpoint kinase 2 | 403642 | 1000 | 384919 | 2161 | |
| CC/S | Chk2 | checkpoint kinase 2 | 404276 | 1001 | 385747 | 2162 | |
| CC/S | Chk2 | checkpoint kinase 2 | 405598 | 1002 | 386087 | 2163 | |
| CC/S | Chk2 | checkpoint kinase 2 | 544772 | 1003 | 442458 | 2164 | |
| CC/S | Claspin | claspin | 251195 | 1004 | 251195 | 2165 | |
| CC/S | Claspin | claspin | 318121 | 1005 | 312995 | 2166 | |
| CC/S | Claspin | claspin | 373220 | 1006 | 362317 | 2167 | |
| CC/S | Claspin | claspin | 544356 | 1007 | 442335 | 2168 | |
| CC/S | Cyclin A | cyclin A2 | 274026 | 1008 | 274026 | 2169 | |
| CC/S | Cyclin B | cyclin B1 | 256442 | 1009 | 256442 | 2170 | |
| CC/S | Cyclin B | cyclin B3 | 276014 | 1010 | 276014 | 2171 | |
| CC/S | Cyclin B | cyclin B2 | 288207 | 1011 | 288207 | 2172 | |
| CC/S | Cyclin B | cyclin B3 | 348603 | 1012 | 338682 | 2173 | |
| CC/S | Cyclin B | cyclin B3 | 376038 | 1013 | 365206 | 2174 | |
| CC/S | Cyclin B | cyclin B3 | 376042 | 1014 | 365210 | 2175 | |
| CC/S | Cyclin B | cyclin B3 | 396540 | 1015 | 379790 | 2176 | |
| CC/S | Cyclin B | cyclin B1 | 505500 | 1016 | 424588 | 2177 | |
| CC/S | Cyclin B | cyclin B1 | 506572 | 1017 | 423387 | 2178 | |
| CC/S | Cyclin D | cyclin D1 | 227507 | 1018 | 227507 | 2179 | |
| CC/S | Cyclin D | cyclin D2 | 261254 | 1019 | 261254 | 2180 | |
| CC/S | Cyclin D | cyclin D3 | 372987 | 1020 | 362078 | 2181 | |
| CC/S | Cyclin D | cyclin D3 | 372988 | 1021 | 362079 | 2182 | |
| CC/S | Cyclin D | cyclin D3 | 372991 | 1022 | 362082 | 2183 | |
| CC/S | Cyclin D | cyclin D3 | 414200 | 1023 | 397545 | 2184 | |
| CC/S | Cyclin D | cyclin D3 | 415497 | 1024 | 401595 | 2185 | |
| CC/S | Cyclin D | cyclin D3 | 505064 | 1025 | 425830 | 2186 | |
| CC/S | Cyclin D | cyclin D3 | 511642 | 1026 | 426212 | 2187 | |
| CC/S | Cyclin D | cyclin D1 | 542897 | 1027 | 441863 | 2188 | |
| CC/S | Cyclin E | cyclin E1 | 262643 | 1028 | 262643 | 2189 | |
| CC/S | Cyclin E | cyclin E2 | 308108 | 1029 | 309181 | 2190 | |
| CC/S | Cyclin E | cyclin E1 | 357943 | 1030 | 350625 | 2191 | |
| CC/S | Cyclin E | cyclin E2 | 396133 | 1031 | 379437 | 2192 | |
| CC/S | Cyclin E | cyclin E1 | 444983 | 1032 | 410179 | 2193 | |
| CC/S | Cyclin E | cyclin E2 | 520509 | 1033 | 429089 | 2194 | |
| CC/S | Cyclin E | cyclin E2 | 542725 | 1034 | 445726 | 2195 | |
| CC/S | DNA-PK | protein kinase, DNA-activated, catalytic polypeptide | 314191 | 1035 | 313420 | 2196 | |
| CC/S | DNA-PK | protein kinase, DNA-activated, catalytic polypeptide | 338368 | 1036 | 345182 | 2197 | |

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|---|---|---|---|---|---|---|---|
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 5, p130-binding | 256117 | 1037 | 256117 | 2198 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 6 | 307236 | 1038 | 302159 | 2199 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 1 | 343380 | 1039 | 345571 | 2200 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 3 | 346618 | 1040 | 262904 | 2201 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 2 | 361729 | 1041 | 355249 | 2202 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 6 | 362009 | 1042 | 355036 | 2203 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 3 | 378646 | 1043 | 367914 | 2204 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 4, p107/p130-binding | 379378 | 1044 | 368686 | 2205 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 6 | 381525 | 1045 | 370936 | 2206 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 5, p130-binding | 416274 | 1046 | 398124 | 2207 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 5, p130-binding | 418930 | 1047 | 414312 | 2208 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 5, p130-binding | 517476 | 1048 | 429120 | 2209 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 5, p130-binding | 518234 | 1049 | 429669 | 2210 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 3 | 535432 | 1050 | 443418 | 2211 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 6 | 542100 | 1051 | 446315 | 2212 | |
| CC/S | E2F1/2/3/4/5/6 | E2F transcription factor 6 | 546212 | 1052 | 438864 | 2213 | |
| CC/S | FANCD2 | Fanconi anemia, complementation group D2 | 287647 | 1053 | 287647 | 2214 | |
| CC/S | FANCD2 | Fanconi anemia, complementation group D2 | 383806 | 1054 | 373317 | 2215 | |
| CC/S | FANCD2 | Fanconi anemia, complementation group D2 | 383807 | 1055 | 373318 | 2216 | |
| CC/S | FANCD2 | Fanconi anemia, complementation group D2 | 419585 | 1056 | 398754 | 2217 | |
| CC/S | FANCL | Fanconi anemia, complementation group L | 233741 | 1057 | 233741 | 2218 | |
| CC/S | FANCL | Fanconi anemia, complementation group L | 540646 | 1058 | 441431 | 2219 | |
| CC/S | GADD45 alpha | growth arrest and DNA-damage-inducible, alpha | 370986 | 1059 | 360025 | 2220 | |
| CC/S | GADD45 beta | growth arrest and DNA-damage-inducible, beta | 215631 | 1060 | 215631 | 2221 | |
| CC/S | GADD45 beta | growth arrest and DNA-damage-inducible, alpha | 370985 | 1061 | 360024 | 2222 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 258148 | 1062 | 258148 | 2223 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 258149 | 1063 | 258149 | 2224 | |

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|---|---|---|---|---|---|---|---|
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 299252 | 1064 | 299252 | 2225 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 311420 | 1065 | 310742 | 2226 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 311440 | 1066 | 311302 | 2227 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 348801 | 1067 | 335096 | 2228 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 350057 | 1068 | 266624 | 2229 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 356290 | 1069 | 348637 | 2230 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 358483 | 1070 | 351270 | 2231 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 360430 | 1071 | 353611 | 2232 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 393410 | 1072 | 377062 | 2233 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 393412 | 1073 | 377064 | 2234 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 393413 | 1074 | 377065 | 2235 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 393415 | 1075 | 377067 | 2236 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 428863 | 1076 | 410694 | 2237 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 462284 | 1077 | 417281 | 2238 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 517852 | 1078 | 430257 | 2239 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 539479 | 1079 | 444430 | 2240 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 540827 | 1080 | 440932 | 2241 | |
| CC/S | MDM2 | Mdm2 p53 binding protein homolog (mouse) | 544648 | 1081 | 443274 | 2242 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 376405 | 1082 | 365587 | 2243 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 376406 | 1083 | 365588 | 2244 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 383566 | 1084 | 373060 | 2245 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 412395 | 1085 | 392833 | 2246 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 413973 | 1086 | 408831 | 2247 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 416368 | 1087 | 410383 | 2248 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 416571 | 1088 | 400979 | 2249 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 417033 | 1089 | 408962 | 2250 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 417228 | 1090 | 400305 | 2251 | |

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|---|---|---|---|---|---|---|---|
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 419172 | 1091 | 398474 | 2252 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 419675 | 1092 | 397642 | 2253 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 420019 | 1093 | 396484 | 2254 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 420320 | 1094 | 416511 | 2255 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 422104 | 1095 | 390375 | 2256 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 422195 | 1096 | 407703 | 2257 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 422266 | 1097 | 411310 | 2258 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 423726 | 1098 | 391230 | 2259 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 424437 | 1099 | 398151 | 2260 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 424507 | 1100 | 388355 | 2261 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 424638 | 1101 | 394074 | 2262 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 425029 | 1102 | 397126 | 2263 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 425072 | 1103 | 396989 | 2264 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 425790 | 1104 | 397021 | 2265 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 427406 | 1105 | 387429 | 2266 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 429610 | 1106 | 406850 | 2267 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 430358 | 1107 | 414163 | 2268 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 431441 | 1108 | 392784 | 2269 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 432998 | 1109 | 405991 | 2270 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 435664 | 1110 | 404318 | 2271 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 435797 | 1111 | 400677 | 2272 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 437759 | 1112 | 387743 | 2273 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 438165 | 1113 | 387706 | 2274 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 440369 | 1114 | 415212 | 2275 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 441397 | 1115 | 390489 | 2276 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 444412 | 1116 | 413610 | 2277 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 445130 | 1117 | 396124 | 2278 | |

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|---|---|---|---|---|---|---|---|
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 445764 | 1118 | 393886 | 2279 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 447192 | 1119 | 405806 | 2280 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 447640 | 1120 | 396389 | 2281 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 448895 | 1121 | 396121 | 2282 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 449153 | 1122 | 409167 | 2283 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 450033 | 1123 | 390040 | 2284 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 452213 | 1124 | 404936 | 2285 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 455729 | 1125 | 404954 | 2286 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 456589 | 1126 | 405350 | 2287 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 546487 | 1127 | 448679 | 2288 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 546539 | 1128 | 448232 | 2289 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 547047 | 1129 | 449059 | 2290 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 547353 | 1130 | 447883 | 2291 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 547681 | 1131 | 447851 | 2292 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 547700 | 1132 | 449083 | 2293 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 547874 | 1133 | 447682 | 2294 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548103 | 1134 | 449499 | 2295 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548112 | 1135 | 448434 | 2296 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548248 | 1136 | 448080 | 2297 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548433 | 1137 | 449971 | 2298 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548542 | 1138 | 446597 | 2299 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548805 | 1139 | 446924 | 2300 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548827 | 1140 | 449201 | 2301 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548893 | 1141 | 447943 | 2302 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 548947 | 1142 | 447711 | 2303 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 549228 | 1143 | 447517 | 2304 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 549382 | 1144 | 449177 | 2305 | |

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|---|---|---|---|---|---|---|---|
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 549428 | 1145 | 447038 | 2306 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 549771 | 1146 | 448812 | 2307 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550004 | 1147 | 447084 | 2308 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550110 | 1148 | 446980 | 2309 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550210 | 1149 | 447697 | 2310 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550408 | 1150 | 447136 | 2311 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550500 | 1151 | 450002 | 2312 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 550688 | 1152 | 448066 | 2313 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551204 | 1153 | 447799 | 2314 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551267 | 1154 | 450198 | 2315 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551460 | 1155 | 449274 | 2316 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551554 | 1156 | 448538 | 2317 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551621 | 1157 | 448285 | 2318 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 551740 | 1158 | 450037 | 2319 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 552263 | 1159 | 447069 | 2320 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 552349 | 1160 | 449892 | 2321 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 552474 | 1161 | 447771 | 2322 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 552522 | 1162 | 449936 | 2323 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 552776 | 1163 | 447825 | 2324 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 553047 | 1164 | 447247 | 2325 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 553048 | 1165 | 447787 | 2326 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 553130 | 1166 | 446809 | 2327 | |
| CC/S | NFBD1 | mediator of DNA-damage checkpoint 1 | 553196 | 1167 | 449586 | 2328 | |
| CC/S | Nibrin | nibrin | 265433 | 1168 | 265433 | 2329 | |
| CC/S | Nibrin | nibrin | 452387 | 1169 | 445213 | 2330 | |
| CC/S | p107 | retinoblastoma-like 1 (p107) | 344359 | 1170 | 343646 | 2331 | |
| CC/S | p107 | retinoblastoma-like 1 (p107) | 373664 | 1171 | 362768 | 2332 | |
| CC/S | p130 | retinoblastoma-like 2 (p130) | 262133 | 1172 | 262133 | 2333 | |
| CC/S | p130 | retinoblastoma-like 2 (p130) | 379935 | 1173 | 369267 | 2334 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CC/S | p130 | retinoblastoma-like 2 (p130) | 544405 | 1174 | 443744 | 2335 | |
| CC/S | p130 | retinoblastoma-like 2 (p130) | 544545 | 1175 | 444685 | 2336 | |
| CC/S | p21 | P21 | NA | 1176 | NA | 2337 | |
| CC/S | PCNA | proliferating cell nuclear antigen | 379143 | 1177 | 368438 | 2338 | |
| CC/S | PCNA | proliferating cell nuclear antigen | 379160 | 1178 | 368458 | 2339 | |
| CC/S | RAD9 | RAD9 homolog A (S. pombe) | 307980 | 1179 | 311360 | 2340 | |
| CC/S | Rb protein | retinoblastoma 1 | 267163 | 1180 | 267163 | 2341 | |
| CC/S | Rb protein | retinoblastoma 1 | 467505 | 1181 | 434702 | 2342 | |
| CC/S | Rb protein | retinoblastoma 1 | 542917 | 1182 | 437642 | 2343 | |
| CC/S | SMC1 | structural maintenance of chromosomes 1A | 322213 | 1183 | 323421 | 2344 | |
| CC/S | SMC1 | structural maintenance of chromosomes 1A | 340213 | 1184 | 344906 | 2345 | |
| CC/S | SMC1 | structural maintenance of chromosomes 1A | 375340 | 1185 | 364489 | 2346 | |
| CC/S | SMC1 | structural maintenance of chromosomes 1A | 428014 | 1186 | 413509 | 2347 | |
| CC/S | USP1 | ubiquitin specific peptidase 1 | 339950 | 1187 | 343526 | 2348 | |
| CC/S | USP1 | ubiquitin specific peptidase 1 | 371146 | 1188 | 360188 | 2349 | |
| CC/S | USP1 | ubiquitin specific peptidase 1 | 452143 | 1189 | 403662 | 2350 | |
| M | 4EBP-1 | eukaryotic translation initiation factor 4E binding protein 1 | 338825 | 1190 | 340691 | 2351 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 354396 | 1191 | 346372 | 2352 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 358595 | 1192 | 351407 | 2353 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 368975 | 1193 | 357971 | 2354 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 394700 | 1194 | 378190 | 2355 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 471844 | 1195 | 425899 | 2356 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 505755 | 1196 | 427571 | 2357 | |
| M | ARNT | aryl hydrocarbon receptor nuclear translocator | 515192 | 1197 | 423851 | 2358 | |
| M | CAIX | carbonic anhydrase IX | 378357 | 1198 | 367608 | 2359 | |
| M | CAIX | carbonic anhydrase IX | 544074 | 1199 | 438541 | 2360 | |
| M | CBP | CREB binding protein | 262367 | 1200 | 262367 | 2361 | |
| M | CBP | CREB binding protein | 323508 | 1201 | 323550 | 2362 | |
| M | CBP | CREB binding protein | 382070 | 1202 | 371502 | 2363 | |
| M | CBP | CREB binding protein | 543883 | 1203 | 441978 | 2364 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 246139 | 1204 | 246139 | 2365 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 373619 | 1205 | 362721 | 2366 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 417400 | 1206 | 414781 | 2367 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 427412 | 1207 | 391407 | 2368 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 429794 | 1208 | 407496 | 2369 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 431381 | 1209 | 388548 | 2370 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 445983 | 1210 | 403274 | 2371 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 450875 | 1211 | 405765 | 2372 | |
| M | CITED1 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 | 453707 | 1212 | 401764 | 2373 | |
| M | CITED2 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2 | 367651 | 1213 | 356623 | 2374 | |
| M | CITED2 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2 | 392312 | 1214 | 376126 | 2375 | |
| M | CITED2 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2 | 536159 | 1215 | 442831 | 2376 | |
| M | CITED2 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2 | 537332 | 1216 | 444198 | 2377 | |
| M | CITED4 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 4 | NA | 1217 | NA | 2378 | |
| M | CITED4 | Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, | 372638 | 1218 | 361721 | 2379 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 4 (CBP/p300 interacting transactivator with ED-rich tail) | | | | | |
| M | COMMD1 | copper metabolism (Murr1) domain containing 1 | 311832 | 1219 | 308236 | 2380 | |
| M | COMMD1 | copper metabolism (Murr1) domain containing 1 | 427417 | 1220 | 413207 | 2381 | |
| M | COMMD1 | copper metabolism (Murr1) domain containing 1 | 444166 | 1221 | 410050 | 2382 | |
| M | COMMD1 | copper metabolism (Murr1) domain containing 1 | 458337 | 1222 | 401236 | 2383 | |
| M | COMMD1 | copper metabolism (Murr1) domain containing 1 | 538736 | 1223 | 438961 | 2384 | |
| M | CREB | cAMP responsive element binding protein 1 | 236996 | 1224 | 236996 | 2385 | |
| M | CREB | cAMP responsive element binding protein 1 | 353267 | 1225 | 236995 | 2386 | |
| M | CREB | cAMP responsive element binding protein 3 | 353704 | 1226 | 342136 | 2387 | |
| M | CREB | cAMP responsive element binding protein 1 | 374397 | 1227 | 363518 | 2388 | |
| M | CREB | cAMP responsive element binding protein 1 | 430624 | 1228 | 405539 | 2389 | |
| M | CREB | cAMP responsive element binding protein 1 | 432329 | 1229 | 387699 | 2390 | |
| M | CREB | cAMP responsive element binding protein 1 | 445803 | 1230 | 407227 | 2391 | |
| M | CREB | cAMP responsive element binding protein 1 | 452474 | 1231 | 392428 | 2392 | |
| M | CREB | cAMP responsive element binding protein 1 | 536726 | 1232 | 445892 | 2393 | |
| M | CREB | cAMP responsive element binding protein 1 | 539789 | 1233 | 440809 | 2394 | |
| M | eIF4E | eukaryotic translation initiation factor 4E | 280892 | 1234 | 280892 | 2395 | |
| M | eIF4E | eukaryotic translation initiation factor 4E | 450253 | 1235 | 389624 | 2396 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 244302 | 1236 | 244302 | 2397 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 291300 | 1237 | 291300 | 2398 | |
| M | FIH | hypoxia inducible factor 1, alpha subunit inhibitor (factor inhibiting HIF) | 299163 | 1238 | 299163 | 2399 | |
| M | HIF3-alpha) | hypoxia inducible factor 3, alpha subunit | 300862 | 1239 | 300862 | 2400 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 339613 | 1240 | 341877 | 2401 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 377670 | 1241 | 366898 | 2402 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 414707 | 1242 | 412808 | 2403 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 420102 | 1243 | 407771 | 2404 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| M | FIH (factor inhibiting HIF) | hypoxia inducible factor 1, alpha subunit inhibitor | 442724 | 1244 | 399734 | 2405 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 457771 | 1245 | 408008 | 2406 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 457865 | 1246 | 394052 | 2407 | |
| M | HIF3-alpha | hypoxia inducible factor 3, alpha subunit | 475432 | 1247 | 432578 | 2408 | |
| M | FIH (factor inhibiting HIF) | hypoxia inducible factor 1, alpha subunit inhibitor | 533589 | 1248 | 433360 | 2409 | |
| M | Grb2 | growth factor receptor-bound protein 2 | 316615 | 1249 | 317360 | 2410 | |
| M | Grb2 | growth factor receptor-bound protein 2 | 316804 | 1250 | 339007 | 2411 | |
| M | Grb2 | growth factor receptor-bound protein 2 | 392562 | 1251 | 376345 | 2412 | |
| M | Grb2 | growth factor receptor-bound protein 2 | 392564 | 1252 | 376347 | 2413 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 316099 | 1253 | 312987 | 2414 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 316673 | 1254 | 315180 | 2415 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 338692 | 1255 | 343807 | 2416 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 415691 | 1256 | 412111 | 2417 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 443598 | 1257 | 410911 | 2418 | |
| M | HNF4alpha | hepatocyte nuclear factor 4, alpha | 457232 | 1258 | 396216 | 2419 | |
| M | HNF4alpha2 | Homo sapiens hepatocyte nuclear factor 4, alpha (HNF4A), transcript variant 2, mRNA | NA | 1259 | NA | 2420 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 275521 | 1260 | 275521 | 2421 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 381083 | 1261 | 370473 | 2422 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 381086 | 1262 | 370476 | 2423 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 417621 | 1263 | 399116 | 2424 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 428530 | 1264 | 390298 | 2425 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 433047 | 1265 | 404461 | 2426 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 438491 | 1266 | 393740 | 2427 | |
| M | IBP3 | insulin-like growth factor binding protein 3 | 442142 | 1267 | 392472 | 2428 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| M | IBP3 | insulin-like growth factor binding protein 3 | 545032 | 1268 | 439999 | 2429 | |
| M | JAB1 | COP9 constitutive photomorphogenic homolog subunit 5 (Arabidopsis) | 357849 | 1269 | 350512 | 2430 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 341183 | 1270 | 339573 | 2431 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 371944 | 1271 | 361012 | 2432 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 371945 | 1272 | 361013 | 2433 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 371946 | 1273 | 361014 | 2434 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 428112 | 1274 | 411135 | 2435 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 496619 | 1275 | 436709 | 2436 | |
| M | MNK1 | MAP kinase interacting serine/threonine kinase 1 | 545730 | 1276 | 440974 | 2437 | |
| M | MNK2 | MAP kinase interacting serine/threonine kinase 2 | 250896 | 1277 | 250896 | 2438 | |
| M | MNK2 | MAP kinase interacting serine/threonine kinase 2 | 309340 | 1278 | 309485 | 2439 | |
| M | MNK2 | MAP kinase interacting serine/threonine kinase 2 | 541165 | 1279 | 438904 | 2440 | |
| M | MNK2 | MAP kinase interacting serine/threonine kinase 2 | 545627 | 1280 | 441245 | 2441 | |
| M | p15(INK4A) | cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) | 276925 | 1281 | 276925 | 2442 | |
| M | p15(INK4A) | cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4) | 380142 | 1282 | 369487 | 2443 | |
| M | p300 | E1A binding protein p300 | 263253 | 1283 | 263253 | 2444 | |
| M | Per1 | period homolog 1 (Drosophila) | 317276 | 1284 | 314420 | 2445 | |
| M | Per1 | period homolog 1 (Drosophila) | 354903 | 1285 | 346979 | 2446 | |
| M | RPS6 | ribosomal protein S6 | 315377 | 1286 | 369743 | 2447 | |
| M | RPS6 | ribosomal protein S6 | 380381 | 1287 | 369741 | 2448 | |
| M | RPS6 | ribosomal protein S6 | 380384 | 1288 | 369745 | 2449 | |
| M | RPS6 | ribosomal protein S6 | 380394 | 1289 | 369757 | 2450 | |
| M | SHARP 1 | basic helix-loop-helix family, member e41 | NA | 1290 | NA | 2451 | |
| M | SHARP 1 (BHLH E41) | basic helix-loop-helix family, member e41 | 242728 | 1291 | 242728 | 2452 | |
| M | SHARP 1 (BHLH E41) | basic helix-loop-helix family, member e41 | 540731 | 1292 | 437369 | 2453 | |
| M | SRC1 | nuclear receptor coactivator 1 | 288599 | 1293 | 288599 | 2454 | |
| M | SRC1 | nuclear receptor coactivator 1 | 348332 | 1294 | 320940 | 2455 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| M | SRC1 | nuclear receptor coactivator 1 | 395856 | 1295 | 379197 | 2456 | |
| M | SRC1 | nuclear receptor coactivator 1 | 405141 | 1296 | 385097 | 2457 | |
| M | SRC1 | nuclear receptor coactivator 1 | 406961 | 1297 | 385216 | 2458 | |
| M | SRC1 | nuclear receptor coactivator 1 | 538539 | 1298 | 444039 | 2459 | |
| M | tuberin | tuberous sclerosis 2 | 219476 | 1299 | 219476 | 2460 | |
| M | tuberin | tuberous sclerosis 2 | 350773 | 1300 | 344383 | 2461 | |
| M | tuberin | tuberous sclerosis 2 | 353929 | 1301 | 248099 | 2462 | |
| M | tuberin | tuberous sclerosis 2 | 382538 | 1302 | 371978 | 2463 | |
| M | tuberin | tuberous sclerosis 2 | 401874 | 1303 | 384468 | 2464 | |
| M | tuberin | tuberous sclerosis 2 | 439673 | 1304 | 399232 | 2465 | |
| | AIFSH | apoptosis-inducing factor, short | NA | 1305 | NA | 2466 | |
| | Angiopoietin1 | Angiopoietin 1 | NA | 1306 | NA | 2467 | 2492 |
| | BMP2 CO | BMP2 CO | NA | 1307 | NA | 2468 | 2493 |
| | c-MYC | v-myc myelocytomatosis viral oncogene homolog (avian) | NA | 1308 | NA | 2469 | |
| | COMMD1 | COMMD1 | NA | 1309 | NA | | |
| | COMMD1 NES deleted | COMMD1 with nuclear export seqences deleted | NA | | NA | 2470 | |
| | COMMD1 NES1 deleted and NLS added | COMMD1 with nuclear export sequences deleted and nuclear localization signals added | NA | | NA | 2471 | |
| | COMMD1 SV40 NLS | COMMD1 with SV40 and nuclear localization signals | NA | | NA | 2472 | |
| | COMMD1wt | COMMD1 wild-type | NA | | NA | 2473 | |
| | GLUT1 | solute carrier family 2 (facilitated glucose transporter), member 1 | NA | 1310 | NA | 2474 | |
| | Granulysin FL15 | Granulysin FL15 | NA | 1311 | NA | 2475 | |
| | Granulysin NS9 | Granulysin NS9 | NA | | NA | 2476 | 2494 |
| | Granulysin S9 | Granulysin S9 | NA | | NA | 2477 | 2495 |
| | HIF1 a | hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor) | NA | 1312 | NA | 2478 | |
| | IL15 | interleukin 15 | NA | 1313 | NA | 2479 | |
| | KGF | fibroblast growth factor 7, | NA | 1314 | NA | 2480 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | precursor; mature is 32-194 | | | | | |
| | MCT4 | solute carrier family 16, member 4 (monocarboxylic acid transporter 5) | NA | 1315 | NA | 2481 | 2496 |
| | MYC inhibitor D | MYC inhibitor D (OMOMyc) | NA | 1316 | NA | 2482 | |
| | MYC inhibitor D_90 | MYC inhibitor D_90 (OmoMyc_90) | NA | | NA | 2483 | |
| | C.A. caspase 3_cleavable | Constitutively active (C.A.) caspase 3 cleavable (RevCasp3_Cleavable) | NA | 1317 | NA | 2484 | |
| | C.A. caspase 3_uncleavable | Constitutively active (C.A.) caspase 3 uncleavable (RevCasp3_UnCleavable) | NA | 1318 | NA | 2485 | |
| | C.A. caspase 6 | Constitutively active (C.A.) caspase 6 (RevCasp6) | NA | 1319 | NA | 2486 | |
| | SIAh1 | siah E3 ubiquitin protein ligase 1 | NA | 1320 | NA | 2487 | |
| | HSV1-tk | Herpes simplex virus 1-thymidine kinase | | | | | |

**[00299]** Shown in Table 7, are familiar cancer syndromes, tumor suppressor genes, function of the tumor suppressor gene, chromosomal location, and tumor type observed. Signal-sensor polynucleotides of the present invention can be designed as a therapeutic for any of those listed in the table.

**Table 7. Familial Cancer Syndrome Targets**

| **Familial Cancer Syndrome** | **Tumor Suppressor Gene** | **Function** | **Chromosomal Location** | **Tumor Types Observed** |
|---|---|---|---|---|
| Li-Fraumeni Syndrome | P53 | cell cycle regulation, apoptosis | 17p13.1 | brain tumors, sarcomas, leukemia, breast cancer |
| Familial Retinoblastoma | RB1 | cell cycle regulation | 13q14.1-q14.2 | retinoblastoma, osteogenic sarcoma |
| Wilms Tumor | WT1 | transcriptional regulation | 11p13 | pediatric kidney cancer, most common form of childhood solid tumor |
| Neurofibromatosis Type 1 | NF1 | catalysis of RAS inactivation | 17q11.2 | neurofibromas, sarcomas, gliomas |

| | | | | |
|---|---|---|---|---|
| Neurofibromatosis Type 2 | NF2 | linkage of cell membrane to actin cytoskeleton | 22q12.2 | Schwann cell tumors, astrocytomas, meningiomas, ependymonas |
| Familial Adenomatous Polyposis | APC | signaling through adhesion molecules to nucleus | 5q21-q22 | colon cancer |
| Tuberous sclerosis 1 | TSC1 | forms complex with TSC2 protein, inhibits signaling to downstream effectors of mTOR | 9q34 | seizures, mental retardation, facial angiofibromas |
| Tuberous sclerosis 2 | TSC2 | forms complex with TSC1 protein, inhibits signaling to downstream effectors of mTOR | 16p13.3 | benign growths (hamartomas) in many tissues, astrocytomas, rhabdomyosarcomas |
| Deleted in Pancreatic Carcinoma 4, Familial juvenile polyposis syndrome | DPC4, also known as SMAD4 | regulation of TGF-β/BMP signal transduction | 18q21.1 | pancreatic carcinoma, colon cancer |
| Deleted in Colorectal Carcinoma | DCC | transmembrane receptor involved in axonal guidance via netrins | 18q21.3 | colorectal cancer |
| Familial Breast Cancer | BRCA1 | functions in transcription, DNA binding, transcription coupled DNA repair, homologous recombination, chromosomal stability, ubiquitination of proteins, and centrosome replication | 17q21 | breast and ovarian cancer |

| | | | | |
|---|---|---|---|---|
| Familial Breast Cancer | BRCA2 (FANCD1) | transcriptional regulation of genes involved in DNA repair and homologous recombination | 13q12.3 | breast and ovarian cancer |
| Cowden syndrome | PTEN | phosphoinositide 3-phosphatase, protein tyrosine phosphatase | 10q23.3 | gliomas, breast cancer, thyroid cancer, head & neck squamous carcinoma |
| Peutz-Jeghers Syndrome (PJS) | STK11 (serine-threonine kinase 11) | phosphorylates and activates AMP-activated kinase (AMPK), AMPK involved in stress responses, lipid and glucose meatabolism | 19p13.3 | hyperpigmentation, multiple hamartomatous polyps, colorectal, breast and ovarian cancers |
| Hereditary Nonpolyposis Colon Cancer type 1, HNPCC1 | MSH2 | DNA mismatch repair | 2p22-p21 | colon cancer |
| Hereditary Nonpolyposis Colon Cancer type 2, HNPCC2 | MLH1 | DNA mismatch repair | 3p21.3 | colon cancer |
| Familial diffuse-type gastric cancer | CDH1 | cell-cell adhesion protein | 16q22.1 | gastric cancer, lobular breast cancer |
| von Hippel-Lindau Syndrome | VHL | regulation of transcription elongation through activation of a ubiquitin ligase complex | 3p26-p25 | renal cancers, hemangioblastomas, pheochromocytoma, retinal angioma |
| Familial Melanoma | CDKN2A | p16INK4 inhibits cell-cycle kinases CDK4 and CDK6; p14ARF binds the p53 stabilizing protein MDM2 | 9p21 | melanoma, pancreatic cancer, others |

| | | | | |
|---|---|---|---|---|
| Gorlin Syndrome: Nevoid basal cell carcinoma syndrome (NBCCS) | PTCH (e.g., PTCH1, PTCH2) | transmembrane receptor for sonic hedgehog (shh), involved in early development through repression of action of smoothened | 9q22.3 | basal cell skin carcinoma |
| Multiple Endocrine Neoplasia Type 1 | MEN1 | intrastrand DNA crosslink repair | 11q13 | parathyroid and pituitary adenomas, islet cell tumors, carcinoid |

**[00300]** In additional to the above mentioned targets, the the oncology-related polypeptides may include any "death signal" protein that can be recognized by active T cells of immune system. Such suicide signal proteins encoded by the sensor-signal polynucleotides can be selectively expressed in particular tissues or cells (e.g. cancer cells) through engineered microRNA binding sites and/or other regulatory elements as described herein. The group of proteins, when they are expressed on the surface of a caner cell, can prime T cell to induce T cell mediated immune response, thus killing the cancer cell. As a non-limiting example, a group of proteins that are known to present a "death signal", include, CD80, CD86, B7 and MHC II, etc.

*Protein Cleavage Signals and Sites*

**[00301]** In one embodiment, the oncology-related polypeptides of the present invention may include at least one protein cleavage signal containing at least one protein cleavage site. The protein cleavage site may be located at the N-terminus, the C-terminus, at any space between the N- and the C- termini such as, but not limited to, half-way between the N- and C-termini, between the N-terminus and the half way point, between the half way point and the C-terminus, and combinations thereof.

**[00302]** The oncology-related polypeptides of the present invention may include, but is not limited to, a proprotein convertase (or prohormone convertase), thrombin or Factor Xa protein cleavage signal. Proprotein convertases are a family of nine proteinases, comprising seven basic amino acid-specific subtilisin-like serine proteinases related to yeast kexin, known as prohormone convertase 1/3 (PC1/3), PC2, furin, PC4, PC5/6, paired basic amino-acid cleaving enzyme 4 (PACE4) and PC7, and two other subtilases

that cleave at non-basic residues, called subtilisin kexin isozyme 1 (SKI-1) and proprotein convertase subtilisin kexin 9 (PCSK9). Non-limiting examples of protein cleavage signal amino acid sequences are listing in Table 8. In Table 8, "X" refers to any amino acid, "n" may be 0, 2, 4 or 6 amino acids and "*" refers to the protein cleavage site. In Table 8, SEQ ID NO: 2499 refers to when n=4 and SEQ ID NO: 2500 refers to when n=6.

**Table 8. Protein Cleavage Site Sequences**

| Protein Cleavage Signal | Amino Acid Cleavage Sequence | SEQ ID NO |
|---|---|---|
| Proprotein convertase | R-X-X-R* | 2497 |
| | R-X-K/R-R* | 2498 |
| | K/R-Xn-K/R* | 2499 or 2500 |
| Thrombin | L-V-P-R*-G-S | 2501 |
| | L-V-P-R* | 2502 |
| | A/F/G/I/L/T/V/M-A/F/G/I/L/T/V/W/A-P-R* | 2503 |
| Factor Xa | I-E-G-R* | 2504 |
| | I-D-G-R* | 2505 |
| | A-E-G-R* | 2506 |
| | A/F/G/I/L/T/V/M-D/E-G-R* | 2507 |

**[00303]** In one embodiment, the signal-sensor primary constructs and the mmRNA of the present invention may be engineered such that the primary construct or mmRNA contains at least one encoded protein cleavage signal. The encoded protein cleavage signal may be located before the start codon, after the start codon, before the coding region, within the coding region such as, but not limited to, half way in the coding region, between the start codon and the half way point, between the half way point and the stop codon, after the coding region, before the stop codon, between two stop codons, after the stop codon and combinations thereof.

**[00304]** In one embodiment, the signal-sensor primary constructs or mmRNA of the present invention may include at least one encoded protein cleavage signal containing at least one protein cleavage site. The encoded protein cleavage signal may include, but is not limited to, a proprotein convertase (or prohormone convertase), thrombin and/or Factor Xa protein cleavage signal. One of skill in the art may use Table 1 above or other known methods to determine the appropriate encoded protein cleavage signal to include

in the signal-sensor primary constructs or mmRNA of the present invention. For example, starting with the signal of Table 8 and considering the codons of Table 1 one can design a signal for the signal-sensor primary construct which can produce a protein signal in the resulting oncology-related polypeptide.

**[00305]** In one embodiment, the oncology-related polypeptides of the present invention include at least one protein cleavage signal and/or site.

**[00306]** As a non-limiting example, U.S. Pat. No. 7,374,930 and U.S. Pub. No. 20090227660, herein incorporated by reference in their entireties, use a furin cleavage site to cleave the N-terminal methionine of GLP-1 in the expression product from the Golgi apparatus of the cells. In one embodiment, the polypeptides of the present invention include at least one protein cleavage signal and/or site with the proviso that the polypeptide is not GLP-1.

**[00307]** In one embodiment, the signal-sensor primary constructs or mmRNA of the present invention includes at least one encoded protein cleavage signal and/or site.

**[00308]** In one embodiment, the signal-sensor primary constructs or mmRNA of the present invention includes at least one encoded protein cleavage signal and/or site with the proviso that the signal-sensor primary construct or mmRNA does not encode GLP-1.

**[00309]** In one embodiment, the signal-sensor primary constructs or mmRNA of the present invention may include more than one coding region. Where multiple coding regions are present in the signal-sensor primary construct or mmRNA of the present invention, the multiple coding regions may be separated by encoded protein cleavage sites. As a non-limiting example, the signal-sensor primary construct or mmRNA may be signed in an ordered pattern. On such pattern follows AXBY form where A and B are coding regions which may be the same or different coding regions and/or may encode the same or different oncology-related polypeptides, and X and Y are encoded protein cleavage signals which may encode the same or different protein cleavage signals. A second such pattern follows the form AXYBZ where A and B are coding regions which may be the same or different coding regions and/or may encode the same or different oncology-related polypeptides, and X, Y and Z are encoded protein cleavage signals which may encode the same or different protein cleavage signals. A third pattern follows the form ABXCY where A, B and C are coding regions which may be the same or

different coding regions and/or may encode the same or different oncology-related polypeptides, and X and Y are encoded protein cleavage signals which may encode the same or different protein cleavage signals.

**[00310]** In one embodiment, the oncology-related polypeptides, signal-sensor primary constructs and mmRNA can also contain sequences that encode protein cleavage sites so that the polypeptides, signal-sensor primary constructs and mmRNA can be released from a carrier region or a fusion partner by treatment with a specific protease for said protein cleavage site.

*microRNA*

**[00311]** microRNAs (or miRNA) are 19-25 nucleotide long noncoding RNAs that bind to the 3′UTR of nucleic acid molecules and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. The modified nucleic acids (mRNA), enhanced modified RNA or ribonucleic acids of the invention may comprise one or more microRNA target sequences, microRNA sequences, or microRNA seeds. Such sequences may correspond to any known microRNA such as those taught in US Publication US2005/0261218 and US Publication US2005/0059005, the contents of which are incorporated herein by reference in their entirety. As a non-limiting embodiment, known microRNAs, their sequences and their binding site sequences in the human genome are listed below in Table 9.

**[00312]** A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence. A microRNA seed may comprise positions 2-8 or 2-7 of the mature microRNA. In some embodiments, a microRNA seed may comprise 7 nucleotides (e.g., nucleotides 2-8 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. In some embodiments, a microRNA seed may comprise 6 nucleotides (e.g., nucleotides 2-7 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. See for example, Grimson A, Farh KK, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP; Mol Cell. 2007 Jul 6;27(1):91-105. The bases of the microRNA seed have complete complementarity with the target sequence. By

engineering microRNA target sequences into the 3′UTR of nucleic acids or mRNA of the invention one can target the molecule for degradation or reduced translation, provided the microRNA in question is available. This process will reduce the hazard of off target effects upon nucleic acid molecule delivery. Identification of microRNA, microRNA target regions, and their expression patterns and role in biology have been reported (Bonauer et al., Curr Drug Targets 2010 11:943-949; Anand and Cheresh Curr Opin Hematol 2011 18:171-176; Contreras and Rao Leukemia 2012 26:404-413 (2011 Dec 20. doi: 10.1038/leu.2011.356); Bartel Cell 2009 136:215-233; Landgraf et al, Cell, 2007 129:1401-1414; Gentner and Naldini, Tissue Antigens. 2012 80:393-403 and all references therein; each of which is herein incorporated by reference in its entirety).

**[00313]** For example, if the signal-sensor polynucleotide is not intended to be delivered to the liver but ends up there, then miR-122, a microRNA abundant in liver, can inhibit the expression of the gene of interest if one or multiple target sites of miR-122 are engineered into the 3′UTR of the signal-sensor polynucleotide. Introduction of one or multiple binding sites for different microRNA can be engineered to further decrease the longevity, stability, and protein translation of a signal-sensor polynucleotide. As used herein, the term “microRNA site” refers to a microRNA target site or a microRNA recognition site, or any nucleotide sequence to which a microRNA binds or associates. It should be understood that “binding” may follow traditional Watson-Crick hybridization rules or may reflect any stable association of the microRNA with the target sequence at or adjacent to the microRNA site.

**[00314]** Conversely, for the purposes of the signal-sensor polynucleotides of the present invention, microRNA binding sites can be engineered out of (i.e. removed from) sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, miR-122 binding sites may be removed to improve protein expression in the liver.

**[00315]** In one embodiment, signal-sensor polynucleotides may include at least one miRNA-binding site in the 3’UTR in order to direct cytotoxic or cytoprotective mRNA therapeutics to specific cells such as, but not limited to, normal and/or cancerous cells (e.g., HEP3B or SNU449). As a non-limiting example, a strong apoptotic signal and at least one miR-122a binding site is encoded by the signal-sensor polynucleotide where the

at least one miR-122a binding site is located in the 3'UTR. As another non-limiting example, apoptosis inducing factor short isoform (AIFsh) and at least one miR-122a binding site is encoded by the signal-sensor polynucleotide where the at least one miR-122a binding site is located in the 3'UTR. As yet another non-limiting example, constitutively active (C.A.) caspase 6 and at least one miR-122a binding site is encoded by the signal-sensor polynucleotide where the at least one miR-122a binding site is located in the 3'UTR. As another non-limiting example, HSV1-tk and at least one miR-122a binding site is encoded by the signal-sensor polynucleotide where the at least one miR-122a binding site is located in the 3'UTR.

**[00316]** In another embodiment, signal-sensor polynucleotides may include three miRNA-binding sites in the 3'UTR in order to direct cytotoxic or cytoprotective mRNA therapeutics to specific cells such as, but not limited to, normal and/or cancerous cells (e.g., HEP3B or SNU449). As a non-limiting example, a strong apoptotic signal and three miR-122a binding sites are encoded by the signal-sensor polynucleotide where the three miR-122a binding sites are located in the 3'UTR. As another non-limiting example, apoptosis inducing factor short isoform (AIFsh) and three miR-122a binding sites are encoded by the signal-sensor polynucleotide where the three miR-122a binding sites are located in the 3'UTR. As yet another non-limiting example, constitutively active (C.A.) caspase 6 and three miR-122a binding sites are encoded by the signal-sensor polynucleotide where the three miR-122a binding sites are located in the 3'UTR. As another non-limiting example, HSV1-tk and and three miR-122a binding sites are encoded by the signal-sensor polynucleotide where the three miR-122a binding sites are located in the 3'UTR.

**[00317]** Regulation of expression in multiple tissues can be accomplished through introduction or removal or one or several microRNA binding sites. Shown below in Table 10 are microRNAs which are differentially expressed in different tissues and cells, and often associated with different types of dieases (e.g.cancer cells). The decision of removal or insertion of microRNA binding sites, or any combination, is dependent on microRNA expression patterns and their profilings in cancer cells.

**[00318]** Examples of tissues where microRNA are known to regulate mRNA, and thereby protein expression, include, but are not limited to, liver (miR-122), muscle (miR-

133, miR-206, miR-208), endothelial cells (miR-17-92, miR-126), myeloid cells (miR-142-3p, miR-142-5p, miR-16, miR-21, miR-223, miR-24, miR-27), nervous system (mir-124a, miR-9), pluripotent cells ( miR-302, miR-367, miR-290, miR-371, miR-373), pancreatic islet cells (miR-375), adipose tissue (let-7, miR-30c), heart (miR-1d, miR-149), kidney (miR-192, miR-194, miR-204), and lung epithelial cells (let-7, miR-133, miR-126).

**[00319]** Specifically, microRNAs are known to be differentially expressed in immune cells (also called hematopoietic cells), such as antigen presenting cells (APCs) (e.g. dendritic cells and macrophages), macrophages, monocytes, B lymphocytes, T lymphocytes, granuocytes, natural killer cells, etc. Immune cell specific microRNAs are involved in immunogenicity, autoimmunity, the immune -response to infection, inflammation, as well as unwanted immune response after gene therapy and tissue/organ transplantation. Immune cells specific microRNAs also regulate many aspects of development, proliferation, differentiation and apoptosis of hematopoietic cells (immune cells). For example, miR-142 and miR-146 are exclusively expressed in the immune cells, particularly abundant in myeloid dendritic cells. Introducing the miR-142 binding site into the 3'-UTR of a signal-sensor polypeptide of the present invention can selectively suppress the gene expression in the antigen presenting cells through miR-142 mediated mRNA degradation, limiting antigen presentation in professional APCs (e.g. dendritic cells) and thereby preventing antigen-mediated immune response after gene delivery (see, Annoni A et al., blood, 2009, 114, 5152-5161, the content of which is herein incorporated by reference in its entirety.)

**[00320]** In one embodiment, microRNAs binding sites that are known to be expressed in immune cells, in particular, the antigen presenting cells, can be engineered into the signal-sensor polynucleotides to suppress the expression of the sensor-signal polynucleotide in APCs through microRNA mediated RNA degradation, subduing the antigen-mediated immune response, while the expression of the sensor-signal polynucleotide is maintained in non-immune cells where the immune cell specific microRNAs are not expressed. For example, to prevent the immunogenic reaction caused by a liver specific protein expression, the miR-122 binding site can be removed and the miR-142 (and/or mirR-146) binding sites can be engineered into the 3-UTR of the signal

–sensor polynucleotide (e.g., see the constructs described in Example 38 and the experiment outlined in Examples 39 and 40).

**[00321]** To further drive the selective degradation and suppression of mRNA in APCs and macrophage, the signal-sensor polynucleotide may include another negative regulatory element in the 3-UTR, either alone or in combination with mir-142 and/or mir-146 binding sites. As a non-limiting example, one regulatory element is the Constitutive Decay Elements (CDEs).

**[00322]** Immune cells specific microRNAs include, but are not limited to, hsa-let-7a-2-3p, hsa-let-7a-3p, hsa-7a-5p, hsa-let-7c, hsa-let-7e-3p, hsa-let-7e-5p, hsa-let-7g-3p, hsa-let-7g-5p, hsa-let-7i-3p, hsa-let-7i-5p, miR-10a-3p, miR-10a-5p, miR-1184, hsa-let-7f-1--3p, hsa-let-7f-2--5p, hsa-let-7f-5p, miR-125b-1-3p, miR-125b-2-3p, miR-125b-5p, miR-1279, miR-130a-3p, miR-130a-5p, miR-132-3p, miR-132-5p, miR-142-3p, miR-142-5p, miR-143-3p, miR-143-5p, miR-146a-3p, miR-146a-5p, miR-146b-3p, miR-146b-5p, miR-147a, miR-147b, miR-148a-5p, miR-148a-3p, miR-150-3p, miR-150-5p, miR-151b, miR-155-3p, miR-155-5p, miR-15a-3p, miR-15a-5p, miR-15b-5p, miR-15b-3p, miR-16-1-3p, miR-16-2-3p, miR-16-5p, miR-17-5p, miR-181a-3p, miR-181a-5p, miR-181a-2-3p, miR-182-3p, miR-182-5p, miR-197-3p, miR-197-5p, miR-21-5p, miR-21-3p, miR-214-3p, miR-214-5p, miR-223-3p, miR-223-5p, miR-221-3p, miR-221-5p, miR-23b-3p, miR-23b-5p, miR-24-1-5p,miR-24-2-5p, miR-24-3p, miR-26a-1-3p, miR-26a-2-3p, miR-26a-5p, miR-26b-3p, miR-26b-5p, miR-27a-3p, miR-27a-5p, miR-27b-3p,miR-27b-5p, miR-28-3p, miR-28-5p, miR-2909, miR-29a-3p, miR-29a-5p, miR-29b-1-5p, miR-29b-2-5p, miR-29c-3p, miR-29c-5p,, miR-30e-3p, miR-30e-5p, miR-331-5p, miR-339-3p, miR-339-5p, miR-345-3p, miR-345-5p, miR-346, miR-34a-3p, miR-34a-5p, , miR-363-3p, miR-363-5p, miR-372, miR-377-3p, miR-377-5p, miR-493-3p, miR-493-5p, miR-542, miR-548b-5p, miR548c-5p, miR-548i, miR-548j, miR-548n, miR-574-3p, miR-598, miR-718, miR-935, miR-99a-3p, miR-99a-5p, miR-99b-3p and miR-99b-5p. Shown below in Table 11 are microRNAs that are enriched in specific types of immune cells. Furthermore, novel miroRNAs are discovered in the immune cells in the art through micro-array hybridization and microtome analysis (Jima DD et al, Blood, 2010, 116:e118-e127; Vaz C et al., BMC Genomics, 2010, 11,288, the content of each of which is incorporated herein by reference in its entirety).

**[00323]** MicroRNAs that are known to be expressed in the liver include, but are not limited to, miR-107, miR-122-3p, miR-122-5p, miR-1228-3p, miR-1228-5p, miR-1249, miR-129-5p, miR-1303, miR-151a-3p, miR-151a-5p, miR-152, miR-194-3p, miR-194-5p, miR-199a-3p, miR-199a-5p, miR-199b-3p, miR-199b-5p, miR-296-5p, miR-557, miR-581, miR-939-3p, miR-939-5p. microRNA binding sites from any liver specific microRNA can be introduced to or removed from the signal-sensor polynucleotides to regulate the expression of the signal-sensor polynucleotides in the liver. Liver specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent an immune reaction against protein expression in the liver.

**[00324]** MicroRNAs that are known to be expressed in the lung include, but are not limited to, let-7a-2-3p, let-7a-3p, let-7a-5p, miR-126-3p, miR-126-5p, miR-127-3p, miR-127-5p, miR-130a-3p, miR-130a-5p, miR-130b-3p, miR-130b-5p, miR-133a, miR-133b, miR-134, miR-18a-3p, miR-18a-5p, miR-18b-3p, miR-18b-5p, miR-24-1-5p, miR-24-2-5p, miR-24-3p, miR-296-3p, miR-296-5p, miR-32-3p, miR-337-3p, miR-337-5p, miR-381-3p, miR-381-5p. MicroRNA binding sites from any lung specific microRNA can be introduced to or removed from the signal-sensor polynucleotide to regulate the expression of the signal-sensor polynucleotide in the lung. Lung specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent an immune reaction against protein expression in the lung.

**[00325]** MicroRNAs that are known to be expressed in the heart include, but are not limited to, miR-1, miR-133a, miR-133b, miR-149-3p, miR-149-5p, miR-186-3p, miR-186-5p, miR-208a, miR-208b, miR-210, miR-296-3p, miR-320, miR-451a, miR-451b, miR-499a-3p, miR-499a-5p, miR-499b-3p, miR-499b-5p, miR-744-3p, miR-744-5p, miR-92b-3p and miR-92b-5p. microRNA binding sites from any heart specific microRNA can be introduced to or removed from the signal-sensor polynucleotides to regulate the expression of the signal-sensor polynucleotides in the heart. Heart specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent an immune reaction against protein expression in the heart.

**[00326]** MicroRNAs that are known to be expressed in the nervous system include, but are not limited to, miR-124-5p, miR-125a-3p, miR-125a-5p, miR-125b-1-3p, miR-125b-2-3p, miR-125b-5p,miR-1271-3p, miR-1271-5p, miR-128, miR-132-5p, miR-135a-3p, miR-135a-5p, miR-135b-3p, miR-135b-5p, miR-137, miR-139-5p, miR-139-3p, miR-149-3p, miR-149-5p, miR-153, miR-181c-3p, miR-181c-5p, miR-183-3p, miR-183-5p, miR-190a, miR-190b, miR-212-3p, miR-212-5p, miR-219-1-3p, miR-219-2-3p, miR-23a-3p, miR-23a-5p,miR-30a-5p, miR-30b-3p, miR-30b-5p, miR-30c-1-3p, miR-30c-2-3p, miR-30c-5p, miR-30d-3p, miR-30d-5p, miR-329, miR-342-3p, miR-3665, miR-3666, miR-380-3p, miR-380-5p, miR-383, miR-410, miR-425-3p, miR-425-5p, miR-454-3p, miR-454-5p, miR-483, miR-510, miR-516a-3p, miR-548b-5p, miR-548c-5p, miR-571, miR-7-1-3p, miR-7-2-3p, miR-7-5p, miR-802, miR-922, miR-9-3p and miR-9-5p. microRNAs enriched in the nervous system further include those specifically expressed in neurons, including, but not limited to, miR-132-3p, miR-132-3p, miR-148b-3p, miR-148b-5p, miR-151a-3p, miR-151a-5p, miR-212-3p, miR-212-5p, miR-320b, miR-320e, miR-323a-3p, miR-323a-5p, miR-324-5p, miR-325, miR-326, miR-328, miR-922 and those specifically expressed in glial cells, including, but not limited to, miR-1250, miR-219-1-3p, miR-219-2-3p, miR-219-5p, miR-23a-3p, miR-23a-5p, miR-3065-3p, miR-3065-5p, miR-30e-3p, miR-30e-5p, miR-32-5p, miR-338-5p, miR-657. microRNA binding sites from any CNS specific microRNA can be introduced to or removed from the signal-sensor polynucleotides to regulate the expression of the signal-sensor polynucleotide in the nervous system. Nervous system specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent an immune reaction against protein expression in the nervous system.

**[00327]** MicroRNAs that are known to be expressed in the pancreas include, but are not limited to, miR-105-3p, miR-105-5p, miR-184, miR-195-3p, miR-195-5p, miR-196a-3p, miR-196a-5p, miR-214-3p, miR-214-5p, miR-216a-3p, miR-216a-5p, miR-30a-3p, miR-33a-3p, miR-33a-5p, miR-375, miR-7-1-3p, miR-7-2-3p, miR-493-3p, miR-493-5p and miR-944. MicroRNA binding sites from any pancreas specific microRNA can be introduced to or removed from the signal-sensor polynucleotide to regulate the expression of the signal-sensor polynucleotide in the pancreas. Pancreas specific

microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent immune reaction against protein expression in the pancreas.

**[00328]** MicroRNAs that are known to be expressed in the kidney further include, but are not limited to, miR-122-3p, miR-145-5p, miR-17-5p, miR-192-3p, miR-192-5p, miR-194-3p, miR-194-5p, miR-20a-3p, miR-20a-5p, miR-204-3p, miR-204-5p, miR-210, miR-216a-3p, miR-216a-5p, miR-296-3p, miR-30a-3p, miR-30a-5p, miR-30b-3p, miR-30b-5p, miR-30c-1-3p, miR-30c-2-3p, miR30c-5p, miR-324-3p, miR-335-3p, miR-335-5p, miR-363-3p, miR-363-5p and miR-562. MicroRNA binding sites from any kidney specific microRNA can be introduced to or removed from the signal-sensor polynucleotide to regulate the expression of the signal-sensor polynucleotide in the kidney. Kidney specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent immune reaction against protein expression in the kidney.

**[00329]** MicroRNAs that are known to be expressed in the muscle further include, but are not limited to, let-7g-3p, let-7g-5p, miR-1, miR-1286, miR-133a, miR-133b, miR-140-3p, miR-143-3p, miR-143-5p, miR-145-3p, miR-145-5p, miR-188-3p, miR-188-5p, miR-206, miR-208a, miR-208b, miR-25-3p and miR-25-5p. MicroRNA binding sites from any muscle specific microRNA can be introduced to or removed from the signal-sensor polynucleotide to regulate the expression of the signal-sensor polynucleotide in the muscle. Muscle specific microRNAs binding sites can be engineered alone or further in combination with immune cells (e.g. APCs) microRNA binding sites in order to prevent an immune reaction against protein expression in the muscle.

**[00330]** MicroRNAs are differentially expressed in different types of cells, such as endothelial cells, epithelial cells and adipocytes. For example, microRNAs that are expressed in endothelial cells include, but are not limited to, let-7b-3p, let-7b-5p, miR-100-3p, miR-100-5p, miR-101-3p, miR-101-5p, miR-126-3p, miR-126-5p, miR-1236-3p, miR-1236-5p, miR-130a-3p, miR-130a-5p, miR-17-5p, miR-17-3p, miR-18a-3p, miR-18a-5p, , miR-19a-3p, miR-19a-5p, miR-19b-1-5p, miR-19b-2-5p, miR-19b-3p, miR-20a-3p, miR-20a-5p, miR-217, miR-210, miR-21-3p, miR-21-5p, miR-221-3p, miR-221-5p, miR-222-3p, miR-222-5p, miR-23a-3p, miR-23a-5p, miR-296-5p, miR-361-3p, miR-

361-5p, miR-421, miR-424-3p, miR-424-5p, miR-513a-5p, miR-92a-1-5p, miR-92a-2-5p, miR-92a-3p, miR-92b-3p and miR-92b-5p. Many novel microRNAs were discovered in endothelial cells from deep-sequencing analysis (Voellenkle C e tal., RNA, 2012, 18, 472-484, herein incorporated by reference in its entirety). MicroRNA binding sites from any endothelial cell specific microRNA can be introduced to or removed from the signal-sensor polynucleotide in order to modulate the expression of the signal-sensor polynucleotide in the endothelial cells in various conditions.

**[00331]** For further example, microRNAs that are expressed in epithelial cells include, but are not limited to, let-7b-3p, let-7b-5p, miR-1246, miR-200a-3p, miR-200a-5p, miR-200b-3p, miR-200b-5p, miR-200c-3p, miR-200c-5p, miR-338-3p, miR-429, miR-451a, miR-451b, miR-494, miR-802 and miR-34a, miR-34b-5p , miR-34c-5p, miR-449a, miR-449b-3p, miR-449b-5p specific in respiratory ciliated epithelial cells; let-7 family, miR-133a, miR-133b, miR-126 specific in lung epithelial cells; miR-382-3p, miR-382-5p specific in renal epithelial cells and miR-762 specific in corneal epithelial cells. MicroRNA binding sites from any epithelial cell specific microRNA can be introduced to or removed from the signal-sensor polynucleotide in order to modulate the expression of the signal-sensor polynucleotide in the epithelial cells in various conditions.

**[00332]** In addition, a large group of microRNAs are enriched in embryonic stem cells, controlling stem cell self-renewal as well as the development and/or differentiation of various cell lineages, such as neural cells, cardiac, hematopoietic cells, skin cells, osteogenic cells and muscle cells (Kuppusamy KT et al., Curr. Mol Med, 2013, 13(5), 757-764; Vidigal JA and Ventura A, Semin Cancer Biol. 2012, 22(5-6), 428-436; Goff LA et al., PLoS One, 2009, 4:e7192; Morin RD et al., Genome Res,2008,18, 610-621; Yoo JK et al., Stem Cells Dev. 2012, 21(11), 2049-2057, each of which is herein incorporated by reference in its entirety). MicroRNAs abundant in embryonic stem cells include, but are not limited to, let-7a-2-3p, let-a-3p, let-7a-5p, let7d-3p, let-7d-5p, miR-103a-2-3p, miR-103a-5p, miR-106b-3p, miR-106b-5p, miR-1246, miR-1275, miR-138-1-3p, miR-138-2-3p, miR-138-5p, miR-154-3p, miR-154-5p, miR-200c-3p, miR-200c-5p, miR-290, miR-301a-3p, miR-301a-5p, miR-302a-3p, miR-302a-5p, miR-302b-3p, miR-302b-5p, miR-302c-3p, miR-302c-5p, miR-302d-3p, miR-302d-5p, miR-302e, miR-367-3p, miR-367-5p, miR-369-3p, miR-369-5p, miR-370, miR-371, miR-373, miR-380-

5p, miR-423-3p, miR-423-5p, miR-486-5p, miR-520c-3p, miR-548e, miR-548f, miR-548g-3p, miR-548g-5p, miR-548i, miR-548k, miR-548l, miR-548m, miR-548n, miR-548o-3p, miR-548o-5p, miR-548p, miR-664a-3p, miR-664a-5p, miR-664b-3p, miR-664b-5p, miR-766-3p, miR-766-5p, miR-885-3p, miR-885-5p,miR-93-3p, miR-93-5p, miR-941,miR-96-3p, miR-96-5p, miR-99b-3p and miR-99b-5p. Many predicted novel microRNAs are discovered by deep sequencing in human embryonic stem cells (Morin RD et al., Genome Res,2008,18, 610-621; Goff LA et al., PLoS One, 2009, 4:e7192; Bar M et al., Stem cells, 2008, 26, 2496-2505, the content of each of which is incorporated herein by references in its entirety).

**[00333]** In one embodiment, the binding sites of embryonic stem cell specific microRNAs can be included in or removed from the 3-UTR of the signal-sensor polynucleotide to modulate the development and/or differentiation of embryonic stem cells, to inhibit the senescence of stem cells in a degenerative condition (e.g. degenerative diseases), or to stimulate the senescence and apoptosis of stem cells in a disease condition (e.g. cancer stem cell).

**[00334]** Many microRNA expression studies have been conducted, and are described in the art, to profile the differential expression of microRNAs in various cancer cells /tissues and other diseases. Some microRNAs are abnormally over-expressed in certain cancer cells and others are under-expressed. For example, microRNAs are differentially expressed in cancer cells (WO2008/154098, US2013/0059015, US2013/0042333, WO2011/157294); cancer stem cells (US2012/0053224); pancreatic cancers and diseases (US2009/0131348, US2011/0171646, US2010/0286232, US8389210); asthma and inflammation (US8415096); prostate cancer (US2013/0053264); hepatocellular carcinoma (WO2012/151212, US2012/0329672, WO2008/054828, US8252538); lung cancer cells (WO2011/076143, WO2013/033640, WO2009/070653, US2010/0323357); cutaneous T cell lymphoma (WO2013/011378); colorectal cancer cells (WO2011/0281756, WO2011/076142); cancer positive lympho nodes (WO2009/100430, US2009/0263803); nasopharyngeal carcinoma (EP2112235); chronic obstructive pulmonary disease (US2012/0264626, US2013/0053263); thyroid cancer (WO2013/066678); ovarian cancer cells ( US2012/0309645, WO2011/095623); breast cancer cells (WO2008/154098, WO2007/081740, US2012/0214699), leukemia and

lymphoma (WO2008/073915, US2009/0092974, US2012/0316081, US2012/0283310, WO2010/018563, the content of each of which is incorporated herein by reference in their entirety).

**[00335]** Specifically, microRNA sites that are over-expressed in certain cancer and/or tumor cells can be removed from the 3-UTR of the signal-sensor polynucleotide encoding the oncology-related polypeptide, restoring the expression suppressed by the over-expressed microRNAs in cancer cells, thus ameliorating the corresponsive biological function, for instance, transcription stimulation and/or repression, cell cycle arrest, apoptosis and cell death. Normal cells and tissues, wherein microRNA expression is not up-regulated, will remain unaffected.

**[00336]** MicroRNA can also regulate complex biological processes such as angiogenesis (miR-132) (Anand and Cheresh Curr Opin Hematol 2011 18:171-176). In the signal-sensor polynucleotides of the invention, binding sites for microRNAs that are involved in such processes may be removed or introduced, in order to tailor the expression of the signal-sensor polynucleotides expression to biologically relevant cell types or to the context of relevant biological processes. In this context, the signal-sensor polynucleotideare defined as auxotrophic signal-sensor polynucleotides.

**[00337]** Table 9 is a non-exhaustive listing of miRs and miR binding sites (miR BS) and their sequences which may be used with the present invention.

**Table 9. Mirs and mir binding sites**

| microRNA | mir SEQ ID | BS SEQ ID | microRNA | mir SEQ ID | BS SEQ ID |
|---|---|---|---|---|---|
| hsa-let-7a-2-3p | 2508 | 3529 | hsa-miR-4471 | 4550 | 5571 |
| hsa-let-7a-3p | 2509 | 3530 | hsa-miR-4472 | 4551 | 5572 |
| hsa-let-7a-5p | 2510 | 3531 | hsa-miR-4473 | 4552 | 5573 |
| hsa-let-7b-3p | 2511 | 3532 | hsa-miR-4474-3p | 4553 | 5574 |
| hsa-let-7b-5p | 2512 | 3533 | hsa-miR-4474-5p | 4554 | 5575 |
| hsa-let-7c | 2513 | 3534 | hsa-miR-4475 | 4555 | 5576 |
| hsa-let-7d-3p | 2514 | 3535 | hsa-miR-4476 | 4556 | 5577 |
| hsa-let-7d-5p | 2515 | 3536 | hsa-miR-4477a | 4557 | 5578 |
| hsa-let-7e-3p | 2516 | 3537 | hsa-miR-4477b | 4558 | 5579 |
| hsa-let-7e-5p | 2517 | 3538 | hsa-miR-4478 | 4559 | 5580 |
| hsa-let-7f-1-3p | 2518 | 3539 | hsa-miR-4479 | 4560 | 5581 |
| hsa-let-7f-2-3p | 2519 | 3540 | hsa-miR-448 | 4561 | 5582 |
| hsa-let-7f-5p | 2520 | 3541 | hsa-miR-4480 | 4562 | 5583 |
| hsa-let-7g-3p | 2521 | 3542 | hsa-miR-4481 | 4563 | 5584 |
| hsa-let-7g-5p | 2522 | 3543 | hsa-miR-4482-3p | 4564 | 5585 |

| | | | | | |
|---|---|---|---|---|---|
| hsa-let-7i-3p | 2523 | 3544 | hsa-miR-4482-5p | 4565 | 5586 |
| hsa-let-7i-5p | 2524 | 3545 | hsa-miR-4483 | 4566 | 5587 |
| hsa-miR-1 | 2525 | 3546 | hsa-miR-4484 | 4567 | 5588 |
| hsa-miR-100-3p | 2526 | 3547 | hsa-miR-4485 | 4568 | 5589 |
| hsa-miR-100-5p | 2527 | 3548 | hsa-miR-4486 | 4569 | 5590 |
| hsa-miR-101-3p | 2528 | 3549 | hsa-miR-4487 | 4570 | 5591 |
| hsa-miR-101-5p | 2529 | 3550 | hsa-miR-4488 | 4571 | 5592 |
| hsa-miR-103a-2-5p | 2530 | 3551 | hsa-miR-4489 | 4572 | 5593 |
| hsa-miR-103a-3p | 2531 | 3552 | hsa-miR-4490 | 4573 | 5594 |
| hsa-miR-103b | 2532 | 3553 | hsa-miR-4491 | 4574 | 5595 |
| hsa-miR-105-3p | 2533 | 3554 | hsa-miR-4492 | 4575 | 5596 |
| hsa-miR-105-5p | 2534 | 3555 | hsa-miR-4493 | 4576 | 5597 |
| hsa-miR-106a-3p | 2535 | 3556 | hsa-miR-4494 | 4577 | 5598 |
| hsa-miR-106a-5p | 2536 | 3557 | hsa-miR-4495 | 4578 | 5599 |
| hsa-miR-106b-3p | 2537 | 3558 | hsa-miR-4496 | 4579 | 5600 |
| hsa-miR-106b-5p | 2538 | 3559 | hsa-miR-4497 | 4580 | 5601 |
| hsa-miR-107 | 2539 | 3560 | hsa-miR-4498 | 4581 | 5602 |
| hsa-miR-10a-3p | 2540 | 3561 | hsa-miR-4499 | 4582 | 5603 |
| hsa-miR-10a-5p | 2541 | 3562 | hsa-miR-449a | 4583 | 5604 |
| hsa-miR-10b-3p | 2542 | 3563 | hsa-miR-449b-3p | 4584 | 5605 |
| hsa-miR-10b-5p | 2543 | 3564 | hsa-miR-449b-5p | 4585 | 5606 |
| hsa-miR-1178-3p | 2544 | 3565 | hsa-miR-449c-3p | 4586 | 5607 |
| hsa-miR-1178-5p | 2545 | 3566 | hsa-miR-449c-5p | 4587 | 5608 |
| hsa-miR-1179 | 2546 | 3567 | hsa-miR-4500 | 4588 | 5609 |
| hsa-miR-1180 | 2547 | 3568 | hsa-miR-4501 | 4589 | 5610 |
| hsa-miR-1181 | 2548 | 3569 | hsa-miR-4502 | 4590 | 5611 |
| hsa-miR-1182 | 2549 | 3570 | hsa-miR-4503 | 4591 | 5612 |
| hsa-miR-1183 | 2550 | 3571 | hsa-miR-4504 | 4592 | 5613 |
| hsa-miR-1184 | 2551 | 3572 | hsa-miR-4505 | 4593 | 5614 |
| hsa-miR-1185-1-3p | 2552 | 3573 | hsa-miR-4506 | 4594 | 5615 |
| hsa-miR-1185-2-3p | 2553 | 3574 | hsa-miR-4507 | 4595 | 5616 |
| hsa-miR-1185-5p | 2554 | 3575 | hsa-miR-4508 | 4596 | 5617 |
| hsa-miR-1193 | 2555 | 3576 | hsa-miR-4509 | 4597 | 5618 |
| hsa-miR-1197 | 2556 | 3577 | hsa-miR-450a-3p | 4598 | 5619 |
| hsa-miR-1200 | 2557 | 3578 | hsa-miR-450a-5p | 4599 | 5620 |
| hsa-miR-1202 | 2558 | 3579 | hsa-miR-450b-3p | 4600 | 5621 |
| hsa-miR-1203 | 2559 | 3580 | hsa-miR-450b-5p | 4601 | 5622 |
| hsa-miR-1204 | 2560 | 3581 | hsa-miR-4510 | 4602 | 5623 |
| hsa-miR-1205 | 2561 | 3582 | hsa-miR-4511 | 4603 | 5624 |
| hsa-miR-1206 | 2562 | 3583 | hsa-miR-4512 | 4604 | 5625 |
| hsa-miR-1207-3p | 2563 | 3584 | hsa-miR-4513 | 4605 | 5626 |
| hsa-miR-1207-5p | 2564 | 3585 | hsa-miR-4514 | 4606 | 5627 |
| hsa-miR-1208 | 2565 | 3586 | hsa-miR-4515 | 4607 | 5628 |
| hsa-miR-122-3p | 2566 | 3587 | hsa-miR-4516 | 4608 | 5629 |
| hsa-miR-1224-3p | 2567 | 3588 | hsa-miR-4517 | 4609 | 5630 |
| hsa-miR-1224-5p | 2568 | 3589 | hsa-miR-4518 | 4610 | 5631 |
| hsa-miR-1225-3p | 2569 | 3590 | hsa-miR-4519 | 4611 | 5632 |
| hsa-miR-1225-5p | 2570 | 3591 | hsa-miR-451a | 4612 | 5633 |
| hsa-miR-122-5p | 2571 | 3592 | hsa-miR-451b | 4613 | 5634 |

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|---|---|---|---|---|---|
| hsa-miR-1226-3p | 2572 | 3593 | hsa-miR-4520a-3p | 4614 | 5635 |
| hsa-miR-1226-5p | 2573 | 3594 | hsa-miR-4520a-5p | 4615 | 5636 |
| hsa-miR-1227-3p | 2574 | 3595 | hsa-miR-4520b-3p | 4616 | 5637 |
| hsa-miR-1227-5p | 2575 | 3596 | hsa-miR-4520b-5p | 4617 | 5638 |
| hsa-miR-1228-3p | 2576 | 3597 | hsa-miR-4521 | 4618 | 5639 |
| hsa-miR-1228-5p | 2577 | 3598 | hsa-miR-4522 | 4619 | 5640 |
| hsa-miR-1229-3p | 2578 | 3599 | hsa-miR-4523 | 4620 | 5641 |
| hsa-miR-1229-5p | 2579 | 3600 | hsa-miR-452-3p | 4621 | 5642 |
| hsa-miR-1231 | 2580 | 3601 | hsa-miR-4524a-3p | 4622 | 5643 |
| hsa-miR-1233-1-5p | 2581 | 3602 | hsa-miR-4524a-5p | 4623 | 5644 |
| hsa-miR-1233-3p | 2582 | 3603 | hsa-miR-4524b-3p | 4624 | 5645 |
| hsa-miR-1234-3p | 2583 | 3604 | hsa-miR-4524b-5p | 4625 | 5646 |
| hsa-miR-1234-5p | 2584 | 3605 | hsa-miR-4525 | 4626 | 5647 |
| hsa-miR-1236-3p | 2585 | 3606 | hsa-miR-452-5p | 4627 | 5648 |
| hsa-miR-1236-5p | 2586 | 3607 | hsa-miR-4526 | 4628 | 5649 |
| hsa-miR-1237-3p | 2587 | 3608 | hsa-miR-4527 | 4629 | 5650 |
| hsa-miR-1237-5p | 2588 | 3609 | hsa-miR-4528 | 4630 | 5651 |
| hsa-miR-1238-3p | 2589 | 3610 | hsa-miR-4529-3p | 4631 | 5652 |
| hsa-miR-1238-5p | 2590 | 3611 | hsa-miR-4529-5p | 4632 | 5653 |
| hsa-miR-1243 | 2591 | 3612 | hsa-miR-4530 | 4633 | 5654 |
| hsa-miR-124-3p | 2592 | 3613 | hsa-miR-4531 | 4634 | 5655 |
| hsa-miR-1244 | 2593 | 3614 | hsa-miR-4532 | 4635 | 5656 |
| hsa-miR-1245a | 2594 | 3615 | hsa-miR-4533 | 4636 | 5657 |
| hsa-miR-1245b-3p | 2595 | 3616 | hsa-miR-4534 | 4637 | 5658 |
| hsa-miR-1245b-5p | 2596 | 3617 | hsa-miR-4535 | 4638 | 5659 |
| hsa-miR-124-5p | 2597 | 3618 | hsa-miR-4536-3p | 4639 | 5660 |
| hsa-miR-1246 | 2598 | 3619 | hsa-miR-4536-5p | 4640 | 5661 |
| hsa-miR-1247-3p | 2599 | 3620 | hsa-miR-4537 | 4641 | 5662 |
| hsa-miR-1247-5p | 2600 | 3621 | hsa-miR-4538 | 4642 | 5663 |
| hsa-miR-1248 | 2601 | 3622 | hsa-miR-4539 | 4643 | 5664 |
| hsa-miR-1249 | 2602 | 3623 | hsa-miR-4540 | 4644 | 5665 |
| hsa-miR-1250 | 2603 | 3624 | hsa-miR-454-3p | 4645 | 5666 |
| hsa-miR-1251 | 2604 | 3625 | hsa-miR-454-5p | 4646 | 5667 |
| hsa-miR-1252 | 2605 | 3626 | hsa-miR-455-3p | 4647 | 5668 |
| hsa-miR-1253 | 2606 | 3627 | hsa-miR-455-5p | 4648 | 5669 |
| hsa-miR-1254 | 2607 | 3628 | hsa-miR-4632-3p | 4649 | 5670 |
| hsa-miR-1255a | 2608 | 3629 | hsa-miR-4632-5p | 4650 | 5671 |
| hsa-miR-1255b-2-3p | 2609 | 3630 | hsa-miR-4633-3p | 4651 | 5672 |
| hsa-miR-1255b-5p | 2610 | 3631 | hsa-miR-4633-5p | 4652 | 5673 |
| hsa-miR-1256 | 2611 | 3632 | hsa-miR-4634 | 4653 | 5674 |
| hsa-miR-1257 | 2612 | 3633 | hsa-miR-4635 | 4654 | 5675 |
| hsa-miR-1258 | 2613 | 3634 | hsa-miR-4636 | 4655 | 5676 |
| hsa-miR-125a-3p | 2614 | 3635 | hsa-miR-4637 | 4656 | 5677 |
| hsa-miR-125a-5p | 2615 | 3636 | hsa-miR-4638-3p | 4657 | 5678 |
| hsa-miR-125b-1-3p | 2616 | 3637 | hsa-miR-4638-5p | 4658 | 5679 |
| hsa-miR-125b-2-3p | 2617 | 3638 | hsa-miR-4639-3p | 4659 | 5680 |
| hsa-miR-125b-5p | 2618 | 3639 | hsa-miR-4639-5p | 4660 | 5681 |
| hsa-miR-1260a | 2619 | 3640 | hsa-miR-4640-3p | 4661 | 5682 |
| hsa-miR-1260b | 2620 | 3641 | hsa-miR-4640-5p | 4662 | 5683 |

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|---|---|---|---|---|---|
| hsa-miR-1261 | 2621 | 3642 | hsa-miR-4641 | 4663 | 5684 |
| hsa-miR-1262 | 2622 | 3643 | hsa-miR-4642 | 4664 | 5685 |
| hsa-miR-1263 | 2623 | 3644 | hsa-miR-4643 | 4665 | 5686 |
| hsa-miR-126-3p | 2624 | 3645 | hsa-miR-4644 | 4666 | 5687 |
| hsa-miR-1264 | 2625 | 3646 | hsa-miR-4645-3p | 4667 | 5688 |
| hsa-miR-1265 | 2626 | 3647 | hsa-miR-4645-5p | 4668 | 5689 |
| hsa-miR-126-5p | 2627 | 3648 | hsa-miR-4646-3p | 4669 | 5690 |
| hsa-miR-1266 | 2628 | 3649 | hsa-miR-4646-5p | 4670 | 5691 |
| hsa-miR-1267 | 2629 | 3650 | hsa-miR-4647 | 4671 | 5692 |
| hsa-miR-1268a | 2630 | 3651 | hsa-miR-4648 | 4672 | 5693 |
| hsa-miR-1268b | 2631 | 3652 | hsa-miR-4649-3p | 4673 | 5694 |
| hsa-miR-1269a | 2632 | 3653 | hsa-miR-4649-5p | 4674 | 5695 |
| hsa-miR-1269b | 2633 | 3654 | hsa-miR-4650-3p | 4675 | 5696 |
| hsa-miR-1270 | 2634 | 3655 | hsa-miR-4650-5p | 4676 | 5697 |
| hsa-miR-1271-3p | 2635 | 3656 | hsa-miR-4651 | 4677 | 5698 |
| hsa-miR-1271-5p | 2636 | 3657 | hsa-miR-4652-3p | 4678 | 5699 |
| hsa-miR-1272 | 2637 | 3658 | hsa-miR-4652-5p | 4679 | 5700 |
| hsa-miR-1273a | 2638 | 3659 | hsa-miR-4653-3p | 4680 | 5701 |
| hsa-miR-1273c | 2639 | 3660 | hsa-miR-4653-5p | 4681 | 5702 |
| hsa-miR-1273d | 2640 | 3661 | hsa-miR-4654 | 4682 | 5703 |
| hsa-miR-1273e | 2641 | 3662 | hsa-miR-4655-3p | 4683 | 5704 |
| hsa-miR-1273f | 2642 | 3663 | hsa-miR-4655-5p | 4684 | 5705 |
| hsa-miR-1273g-3p | 2643 | 3664 | hsa-miR-4656 | 4685 | 5706 |
| hsa-miR-1273g-5p | 2644 | 3665 | hsa-miR-4657 | 4686 | 5707 |
| hsa-miR-127-3p | 2645 | 3666 | hsa-miR-4658 | 4687 | 5708 |
| hsa-miR-1275 | 2646 | 3667 | hsa-miR-4659a-3p | 4688 | 5709 |
| hsa-miR-127-5p | 2647 | 3668 | hsa-miR-4659a-5p | 4689 | 5710 |
| hsa-miR-1276 | 2648 | 3669 | hsa-miR-4659b-3p | 4690 | 5711 |
| hsa-miR-1277-3p | 2649 | 3670 | hsa-miR-4659b-5p | 4691 | 5712 |
| hsa-miR-1277-5p | 2650 | 3671 | hsa-miR-466 | 4692 | 5713 |
| hsa-miR-1278 | 2651 | 3672 | hsa-miR-4660 | 4693 | 5714 |
| hsa-miR-1279 | 2652 | 3673 | hsa-miR-4661-3p | 4694 | 5715 |
| hsa-miR-128 | 2653 | 3674 | hsa-miR-4661-5p | 4695 | 5716 |
| hsa-miR-1281 | 2654 | 3675 | hsa-miR-4662a-3p | 4696 | 5717 |
| hsa-miR-1282 | 2655 | 3676 | hsa-miR-4662a-5p | 4697 | 5718 |
| hsa-miR-1283 | 2656 | 3677 | hsa-miR-4662b | 4698 | 5719 |
| hsa-miR-1284 | 2657 | 3678 | hsa-miR-4663 | 4699 | 5720 |
| hsa-miR-1285-3p | 2658 | 3679 | hsa-miR-4664-3p | 4700 | 5721 |
| hsa-miR-1285-5p | 2659 | 3680 | hsa-miR-4664-5p | 4701 | 5722 |
| hsa-miR-1286 | 2660 | 3681 | hsa-miR-4665-3p | 4702 | 5723 |
| hsa-miR-1287 | 2661 | 3682 | hsa-miR-4665-5p | 4703 | 5724 |
| hsa-miR-1288 | 2662 | 3683 | hsa-miR-4666a-3p | 4704 | 5725 |
| hsa-miR-1289 | 2663 | 3684 | hsa-miR-4666a-5p | 4705 | 5726 |
| hsa-miR-1290 | 2664 | 3685 | hsa-miR-4666b | 4706 | 5727 |
| hsa-miR-1291 | 2665 | 3686 | hsa-miR-4667-3p | 4707 | 5728 |
| hsa-miR-129-1-3p | 2666 | 3687 | hsa-miR-4667-5p | 4708 | 5729 |
| hsa-miR-1292-3p | 2667 | 3688 | hsa-miR-4668-3p | 4709 | 5730 |
| hsa-miR-129-2-3p | 2668 | 3689 | hsa-miR-4668-5p | 4710 | 5731 |
| hsa-miR-1292-5p | 2669 | 3690 | hsa-miR-4669 | 4711 | 5732 |

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|---|---|---|---|---|---|
| hsa-miR-1293 | 2670 | 3691 | hsa-miR-4670-3p | 4712 | 5733 |
| hsa-miR-1294 | 2671 | 3692 | hsa-miR-4670-5p | 4713 | 5734 |
| hsa-miR-1295a | 2672 | 3693 | hsa-miR-4671-3p | 4714 | 5735 |
| hsa-miR-1295b-3p | 2673 | 3694 | hsa-miR-4671-5p | 4715 | 5736 |
| hsa-miR-1295b-5p | 2674 | 3695 | hsa-miR-4672 | 4716 | 5737 |
| hsa-miR-129-5p | 2675 | 3696 | hsa-miR-4673 | 4717 | 5738 |
| hsa-miR-1296 | 2676 | 3697 | hsa-miR-4674 | 4718 | 5739 |
| hsa-miR-1297 | 2677 | 3698 | hsa-miR-4675 | 4719 | 5740 |
| hsa-miR-1298 | 2678 | 3699 | hsa-miR-4676-3p | 4720 | 5741 |
| hsa-miR-1299 | 2679 | 3700 | hsa-miR-4676-5p | 4721 | 5742 |
| hsa-miR-1301 | 2680 | 3701 | hsa-miR-4677-3p | 4722 | 5743 |
| hsa-miR-1302 | 2681 | 3702 | hsa-miR-4677-5p | 4723 | 5744 |
| hsa-miR-1303 | 2682 | 3703 | hsa-miR-4678 | 4724 | 5745 |
| hsa-miR-1304-3p | 2683 | 3704 | hsa-miR-4679 | 4725 | 5746 |
| hsa-miR-1304-5p | 2684 | 3705 | hsa-miR-4680-3p | 4726 | 5747 |
| hsa-miR-1305 | 2685 | 3706 | hsa-miR-4680-5p | 4727 | 5748 |
| hsa-miR-1306-3p | 2686 | 3707 | hsa-miR-4681 | 4728 | 5749 |
| hsa-miR-1306-5p | 2687 | 3708 | hsa-miR-4682 | 4729 | 5750 |
| hsa-miR-1307-3p | 2688 | 3709 | hsa-miR-4683 | 4730 | 5751 |
| hsa-miR-1307-5p | 2689 | 3710 | hsa-miR-4684-3p | 4731 | 5752 |
| hsa-miR-130a-3p | 2690 | 3711 | hsa-miR-4684-5p | 4732 | 5753 |
| hsa-miR-130a-5p | 2691 | 3712 | hsa-miR-4685-3p | 4733 | 5754 |
| hsa-miR-130b-3p | 2692 | 3713 | hsa-miR-4685-5p | 4734 | 5755 |
| hsa-miR-130b-5p | 2693 | 3714 | hsa-miR-4686 | 4735 | 5756 |
| hsa-miR-1321 | 2694 | 3715 | hsa-miR-4687-3p | 4736 | 5757 |
| hsa-miR-1322 | 2695 | 3716 | hsa-miR-4687-5p | 4737 | 5758 |
| hsa-miR-1323 | 2696 | 3717 | hsa-miR-4688 | 4738 | 5759 |
| hsa-miR-132-3p | 2697 | 3718 | hsa-miR-4689 | 4739 | 5760 |
| hsa-miR-1324 | 2698 | 3719 | hsa-miR-4690-3p | 4740 | 5761 |
| hsa-miR-132-5p | 2699 | 3720 | hsa-miR-4690-5p | 4741 | 5762 |
| hsa-miR-133a | 2700 | 3721 | hsa-miR-4691-3p | 4742 | 5763 |
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| hsa-miR-4311 | 3443 | 4464 | hsa-miR-675-5p | 5485 | 6506 |
| hsa-miR-4312 | 3444 | 4465 | hsa-miR-676-3p | 5486 | 6507 |
| hsa-miR-4313 | 3445 | 4466 | hsa-miR-676-5p | 5487 | 6508 |
| hsa-miR-431-3p | 3446 | 4467 | hsa-miR-708-3p | 5488 | 6509 |
| hsa-miR-4314 | 3447 | 4468 | hsa-miR-708-5p | 5489 | 6510 |
| hsa-miR-4315 | 3448 | 4469 | hsa-miR-711 | 5490 | 6511 |
| hsa-miR-431-5p | 3449 | 4470 | hsa-miR-7-1-3p | 5491 | 6512 |
| hsa-miR-4316 | 3450 | 4471 | hsa-miR-718 | 5492 | 6513 |
| hsa-miR-4317 | 3451 | 4472 | hsa-miR-7-2-3p | 5493 | 6514 |
| hsa-miR-4318 | 3452 | 4473 | hsa-miR-744-3p | 5494 | 6515 |
| hsa-miR-4319 | 3453 | 4474 | hsa-miR-744-5p | 5495 | 6516 |

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|---|---|---|---|---|---|
| hsa-miR-4320 | 3454 | 4475 | hsa-miR-758-3p | 5496 | 6517 |
| hsa-miR-4321 | 3455 | 4476 | hsa-miR-758-5p | 5497 | 6518 |
| hsa-miR-4322 | 3456 | 4477 | hsa-miR-759 | 5498 | 6519 |
| hsa-miR-4323 | 3457 | 4478 | hsa-miR-7-5p | 5499 | 6520 |
| hsa-miR-432-3p | 3458 | 4479 | hsa-miR-760 | 5500 | 6521 |
| hsa-miR-4324 | 3459 | 4480 | hsa-miR-761 | 5501 | 6522 |
| hsa-miR-4325 | 3460 | 4481 | hsa-miR-762 | 5502 | 6523 |
| hsa-miR-432-5p | 3461 | 4482 | hsa-miR-764 | 5503 | 6524 |
| hsa-miR-4326 | 3462 | 4483 | hsa-miR-765 | 5504 | 6525 |
| hsa-miR-4327 | 3463 | 4484 | hsa-miR-766-3p | 5505 | 6526 |
| hsa-miR-4328 | 3464 | 4485 | hsa-miR-766-5p | 5506 | 6527 |
| hsa-miR-4329 | 3465 | 4486 | hsa-miR-767-3p | 5507 | 6528 |
| hsa-miR-433 | 3466 | 4487 | hsa-miR-767-5p | 5508 | 6529 |
| hsa-miR-4330 | 3467 | 4488 | hsa-miR-769-3p | 5509 | 6530 |
| hsa-miR-4417 | 3468 | 4489 | hsa-miR-769-5p | 5510 | 6531 |
| hsa-miR-4418 | 3469 | 4490 | hsa-miR-770-5p | 5511 | 6532 |
| hsa-miR-4419a | 3470 | 4491 | hsa-miR-802 | 5512 | 6533 |
| hsa-miR-4419b | 3471 | 4492 | hsa-miR-873-3p | 5513 | 6534 |
| hsa-miR-4420 | 3472 | 4493 | hsa-miR-873-5p | 5514 | 6535 |
| hsa-miR-4421 | 3473 | 4494 | hsa-miR-874 | 5515 | 6536 |
| hsa-miR-4422 | 3474 | 4495 | hsa-miR-875-3p | 5516 | 6537 |
| hsa-miR-4423-3p | 3475 | 4496 | hsa-miR-875-5p | 5517 | 6538 |
| hsa-miR-4423-5p | 3476 | 4497 | hsa-miR-876-3p | 5518 | 6539 |
| hsa-miR-4424 | 3477 | 4498 | hsa-miR-876-5p | 5519 | 6540 |
| hsa-miR-4425 | 3478 | 4499 | hsa-miR-877-3p | 5520 | 6541 |
| hsa-miR-4426 | 3479 | 4500 | hsa-miR-877-5p | 5521 | 6542 |
| hsa-miR-4427 | 3480 | 4501 | hsa-miR-885-3p | 5522 | 6543 |
| hsa-miR-4428 | 3481 | 4502 | hsa-miR-885-5p | 5523 | 6544 |
| hsa-miR-4429 | 3482 | 4503 | hsa-miR-887 | 5524 | 6545 |
| hsa-miR-4430 | 3483 | 4504 | hsa-miR-888-3p | 5525 | 6546 |
| hsa-miR-4431 | 3484 | 4505 | hsa-miR-888-5p | 5526 | 6547 |
| hsa-miR-4432 | 3485 | 4506 | hsa-miR-889 | 5527 | 6548 |
| hsa-miR-4433-3p | 3486 | 4507 | hsa-miR-890 | 5528 | 6549 |
| hsa-miR-4433-5p | 3487 | 4508 | hsa-miR-891a | 5529 | 6550 |
| hsa-miR-4434 | 3488 | 4509 | hsa-miR-891b | 5530 | 6551 |
| hsa-miR-4435 | 3489 | 4510 | hsa-miR-892a | 5531 | 6552 |
| hsa-miR-4436a | 3490 | 4511 | hsa-miR-892b | 5532 | 6553 |
| hsa-miR-4436b-3p | 3491 | 4512 | hsa-miR-892c-3p | 5533 | 6554 |
| hsa-miR-4436b-5p | 3492 | 4513 | hsa-miR-892c-5p | 5534 | 6555 |
| hsa-miR-4437 | 3493 | 4514 | hsa-miR-920 | 5535 | 6556 |
| hsa-miR-4438 | 3494 | 4515 | hsa-miR-921 | 5536 | 6557 |
| hsa-miR-4439 | 3495 | 4516 | hsa-miR-922 | 5537 | 6558 |
| hsa-miR-4440 | 3496 | 4517 | hsa-miR-924 | 5538 | 6559 |
| hsa-miR-4441 | 3497 | 4518 | hsa-miR-92a-1-5p | 5539 | 6560 |
| hsa-miR-4442 | 3498 | 4519 | hsa-miR-92a-2-5p | 5540 | 6561 |
| hsa-miR-4443 | 3499 | 4520 | hsa-miR-92a-3p | 5541 | 6562 |
| hsa-miR-4444 | 3500 | 4521 | hsa-miR-92b-3p | 5542 | 6563 |
| hsa-miR-4445-3p | 3501 | 4522 | hsa-miR-92b-5p | 5543 | 6564 |
| hsa-miR-4445-5p | 3502 | 4523 | hsa-miR-933 | 5544 | 6565 |

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|---|---|---|---|---|---|
| hsa-miR-4446-3p | 3503 | 4524 | hsa-miR-93-3p | 5545 | 6566 |
| hsa-miR-4446-5p | 3504 | 4525 | hsa-miR-934 | 5546 | 6567 |
| hsa-miR-4447 | 3505 | 4526 | hsa-miR-935 | 5547 | 6568 |
| hsa-miR-4448 | 3506 | 4527 | hsa-miR-93-5p | 5548 | 6569 |
| hsa-miR-4449 | 3507 | 4528 | hsa-miR-936 | 5549 | 6570 |
| hsa-miR-4450 | 3508 | 4529 | hsa-miR-937-3p | 5550 | 6571 |
| hsa-miR-4451 | 3509 | 4530 | hsa-miR-937-5p | 5551 | 6572 |
| hsa-miR-4452 | 3510 | 4531 | hsa-miR-938 | 5552 | 6573 |
| hsa-miR-4453 | 3511 | 4532 | hsa-miR-939-3p | 5553 | 6574 |
| hsa-miR-4454 | 3512 | 4533 | hsa-miR-939-5p | 5554 | 6575 |
| hsa-miR-4455 | 3513 | 4534 | hsa-miR-9-3p | 5555 | 6576 |
| hsa-miR-4456 | 3514 | 4535 | hsa-miR-940 | 5556 | 6577 |
| hsa-miR-4457 | 3515 | 4536 | hsa-miR-941 | 5557 | 6578 |
| hsa-miR-4458 | 3516 | 4537 | hsa-miR-942 | 5558 | 6579 |
| hsa-miR-4459 | 3517 | 4538 | hsa-miR-943 | 5559 | 6580 |
| hsa-miR-4460 | 3518 | 4539 | hsa-miR-944 | 5560 | 6581 |
| hsa-miR-4461 | 3519 | 4540 | hsa-miR-95 | 5561 | 6582 |
| hsa-miR-4462 | 3520 | 4541 | hsa-miR-9-5p | 5562 | 6583 |
| hsa-miR-4463 | 3521 | 4542 | hsa-miR-96-3p | 5563 | 6584 |
| hsa-miR-4464 | 3522 | 4543 | hsa-miR-96-5p | 5564 | 6585 |
| hsa-miR-4465 | 3523 | 4544 | hsa-miR-98-3p | 5565 | 6586 |
| hsa-miR-4466 | 3524 | 4545 | hsa-miR-98-5p | 5566 | 6587 |
| hsa-miR-4467 | 3525 | 4546 | hsa-miR-99a-3p | 5567 | 6588 |
| hsa-miR-4468 | 3526 | 4547 | hsa-miR-99a-5p | 5568 | 6589 |
| hsa-miR-4469 | 3527 | 4548 | hsa-miR-99b-3p | 5569 | 6590 |
| hsa-miR-4470 | 3528 | 4549 | hsa-miR-99b-5p | 5570 | 6591 |

**[00338]** As shown in Table 10, microRNAs are differentially expressed in different tissues and cells, and often associated with different types of dieases (e.g.cancer cells). The decision of removal or insertion of microRNA binding sites, or any combination, is dependent on microRNA expression patterns and their profilings in cancer cells. In Table 10, "HCC" represents hepatocellular carcinoma, "ALL" stands for acute lymphoblastsic leukemia, "RCC" stands for renal cell carcinoma, "CLL" stands for chrominc lymphocytic leukemia and "MALT" stands for mucosa-associated lymphoid tissue.

**Table 10. mirs, tissues/cell expression and diseases**

| **microRNA** | **mir SEQ ID** | **BS SEQ ID** | **Tissues/cells** | **Associated Disease** | **Biological Function** |
|---|---|---|---|---|---|
| hsa-let-7a-2-3p | 2508 | 3529 | Embryonic stem cells, lung, myeloid cells | inflammatory, various cancers (lung, cervical, breast, pancreatic, | tumor suppressor |

| | | | | | |
|---|---|---|---|---|---|
| | | | | etc) | |
| hsa-let-7a-3p | 2509 | 3530 | Embryonic stem cells, lung | inflammatory, various cancers (lung, cervical, breast, pancreatic, etc) | tumor suppressor |
| hsa-let-7a-5p | 2510 | 3531 | Embryonic stem cells, lung | inflammatory, various cancers (lung, cervical, breast, pancreatic, etc) | tumor suppressor |
| hsa-let-7b-3p | 2511 | 3532 | epithelial cells, endothelial cells (vascular) | lung cancer, colorectal cancer, cervical cancer, inflammation and immune response after infection | tumor angiogenesis |
| hsa-let-7b-5p | 2512 | 3533 | epithelial cells, endothelial cells (vascular) | cervical cancer, inflammation and immune response after infection | tumor angiogenesis |
| hsa-let-7c | 2513 | 3534 | dendritic cells | various cacners (cervical, pancreatic, lung , esopphageal, etc) | tumor suppressor, apoptosis |
| hsa-let-7d-3p | 2514 | 3535 | embryonic stem cells | associated with various cancer cells | tumor suppressor |
| hsa-let-7d-5p | 2515 | 3536 | embryonic stem cells | associated with various cancer cells | tumor suppressor |
| hsa-let-7e-3p | 2516 | 3537 | immune cells | various cancer cells, autoimmunity, endotoxin tolerance | tumor suppressor |
| hsa-let-7e-5p | 2517 | 3538 | immune cells | various cancer cells | tumor suppressor |
| hsa-let-7f-1-3p | 2518 | 3539 | immune cells (T cells) | various cancer cells | tumor suppressor |
| hsa-let-7f-2-3p | 2519 | 3540 | immune cells (T cells) | various cancer cells | tumor suppressor |
| hsa-let-7f-5p | 2520 | 3541 | immune cells (T cells) | Various cancer cells | tumor suppressor |
| hsa-let-7g-3p | 2521 | 3542 | hematopoietic cells, adipose, smooth muscle cells | various cancer cells (lung, breast, etc) | tumor suppressor |
| hsa-let-7g-5p | 2522 | 3543 | hematopoietic cells, adipose, smooth muscle cells | various cancer cells (lung, breast, etc) | tumor suppressor |
| hsa-let-7i-3p | 2523 | 3544 | immune cells | chronic lymphocyte leukimia | tumor suppressor |
| hsa-let-7i-5p | 2524 | 3545 | immune cells | chronic | tumor |

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|---|---|---|---|---|---|
| | | | | lymphocyte leukimia | suppressor |
| hsa-miR-1 | 2525 | 3546 | muscle, heart | | angiogenesis, cell proliferation(myogenesis) |
| hsa-miR-100-3p | 2526 | 3547 | hematopoietic cells, endothelial cells | gastric cancer, pancreatic cancer | tumor angiogenesis |
| hsa-miR-100-5p | 2527 | 3548 | hematopoietic cells, endothelial cells | gastric cancer, pancreatic cancer | tumor angiogenesis |
| hsa-miR-101-3p | 2528 | 3549 | endothelial cells | various cancers (breast,non-small cell lung, colon, gastric, pancreatic, bladder, etc); lupus erythematosus | angiogenesis |
| hsa-miR-101-5p | 2529 | 3550 | endothelial cells | various cancers (breast,non-small cell lung, colon, gastric, pancreatic, bladder, etc); lupus erythematosus | angiogenesis |
| hsa-miR-103a-2-5p | 2530 | 3551 | embryonic stem cells, many tissues/cells | various cancers (endometrial, neuroblastoma, colorectal, breast, liver, etc) | oncogene, cell growth |
| hsa-miR-103a-3p | 2531 | 3552 | embryonic stem cells, many tissues/cells | various cancers (endometrial, neuroblastoma, colorectal, breast, liver, etc) | oncogene, cell growth |
| hsa-miR-103b | 2532 | 3553 | Many tissues/cells | various cancers (endometrial, neuroblastoma, colorectal, breast, liver, etc) | oncogene, cell growth |
| hsa-miR-105-3p | 2533 | 3554 | pancreatic cells | | |
| hsa-miR-105-5p | 2534 | 3555 | pancreatic cells | | |
| hsa-miR-106a-3p | 2535 | 3556 | osteogenic cells | osteocarcoma, other cancers | cell differentiation |
| hsa-miR-106a-5p | 2536 | 3557 | osteogenic cells | osteocarcoma, other cancers | cell differentiation |
| hsa-miR-106b-3p | 2537 | 3558 | embryonic stem cells | various cancers (non-small lung cancer, gastric cancer, HCC, gliomas, etc) | oncogene |
| hsa-miR-106b-5p | 2538 | 3559 | embryonic stem cells | various cancers (non-small lung | oncogene |

| | | | | | |
|---|---|---|---|---|---|
| | | | | cancer, gastric cancer, HCC, gliomas, etc) | |
| hsa-miR-107 | 2539 | 3560 | many tissues, brain hepatocytes/liver | breast cancer, pituitary adenoma, obesity/diabetes | |
| hsa-miR-10a-3p | 2540 | 3561 | hematopoeitic cells | acute myeoid leukemia | oncogene, cell growth |
| hsa-miR-10a-5p | 2541 | 3562 | hematopoeitic cells | acute myeoid leukemia | oncogene, cell growth |
| hsa-miR-10b-3p | 2542 | 3563 | multiple tissues and cells | various cancers (breast, ovarian, glioblastoma, pancreatc ductal adenocarcinoma, gastric, etc) | oncogene |
| hsa-miR-10b-5p | 2543 | 3564 | multiple tissues and cells | various cancers (breast, ovarian, glioblastoma, pancreatc ductal adenocarcinoma, gastric, etc) | oncogene |
| hsa-miR-1178-3p | 2544 | 3565 | | osteocarcoma | |
| hsa-miR-1178-5p | 2545 | 3566 | | osteocarcoma | |
| hsa-miR-1179 | 2546 | 3567 | | osteocarcoma | |
| hsa-miR-1180 | 2547 | 3568 | discovered in sarcoma, no expression data | | |
| hsa-miR-1181 | 2548 | 3569 | | downregulated in ovarian cancer cells, associated with HCV infection in hepatocytes | |
| hsa-miR-1182 | 2549 | 3570 | placenta | | |
| hsa-miR-1183 | 2550 | 3571 | | associated with rectal cancer | |
| hsa-miR-1184 | 2551 | 3572 | Hematopoietic cells | downregulated in oral leukoplakia (OLK) | |
| hsa-miR-1185-1-3p | 2552 | 3573 | placenta | | |
| hsa-miR-1185-2-3p | 2553 | 3574 | placenta | | |
| hsa-miR-1185-5p | 2554 | 3575 | placenta | | |
| hsa-miR-1193 | 2555 | 3576 | | melanoma | |
| hsa-miR-1197 | 2556 | 3577 | | neublastoma | |
| hsa-miR-1200 | 2557 | 3578 | | chronic lynphocytic leukemia | |
| hsa-miR-1202 | 2558 | 3579 | | chronic lynphocytic | |

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|---|---|---|---|---|---|
| | | | | leukemia, downregulated in ovarian cancer cells | |
| hsa-miR-1203 | 2559 | 3580 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1204 | 2560 | 3581 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1205 | 2561 | 3582 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1206 | 2562 | 3583 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1207-3p | 2563 | 3584 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1207-5p | 2564 | 3585 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-1208 | 2565 | 3586 | | in the chromosome 8q24 region, cancer cells | |
| hsa-miR-122-3p | 2566 | 3587 | kidney, liver/hepatocytes | Renal Cell Carcinoma (RCC), cancer cells | lipid metabolism |
| hsa-miR-1224-3p | 2567 | 3588 | | Lupus nephritis | |
| hsa-miR-1224-5p | 2568 | 3589 | | rectal cancer | |
| hsa-miR-1225-3p | 2569 | 3590 | | adrenal pheochromocytomas; upregulated in MITF KnockDown melanocytes | |
| hsa-miR-1225-5p | 2570 | 3591 | | prostate cancer | |
| hsa-miR-122-5p | 2571 | 3592 | liver/hepatocytes | cancer cells | lipid metabolism |
| hsa-miR-1226-3p | 2572 | 3593 | discovered in a mirtron screening | | |
| hsa-miR-1226-5p | 2573 | 3594 | discovered in a mirtron screening | | |
| hsa-miR-1227-3p | 2574 | 3595 | cartilage/chondrocytes | | |
| hsa-miR-1227-5p | 2575 | 3596 | cartilage/chondrocy | | |

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|---|---|---|---|---|---|
| | | | tes | | |
| hsa-miR-1228-3p | 2576 | 3597 | liver(hepatocytes) | Hepatocellular carcinoma(HCC) | anti-apoptosis |
| hsa-miR-1228-5p | 2577 | 3598 | liver(hepatocytes) | Hepatocellular carcinoma(HCC) | anti-apoptosis |
| hsa-miR-1229-3p | 2578 | 3599 | discovered in a mirtron screening | | |
| hsa-miR-1229-5p | 2579 | 3600 | discovered in a mirtron screening | | |
| hsa-miR-1231 | 2580 | 3601 | | HCC | |
| hsa-miR-1233-1-5p | 2581 | 3602 | serum | | |
| hsa-miR-1233-3p | 2582 | 3603 | serum | | |
| hsa-miR-1234-3p | 2583 | 3604 | discovered in embryonic stem cell | | |
| hsa-miR-1234-5p | 2584 | 3605 | discovered in embryonic stem cell | | |
| hsa-miR-1236-3p | 2585 | 3606 | lymphatic endothelial cells | | target to VEGFR-3 |
| hsa-miR-1236-5p | 2586 | 3607 | lymphatic endothelial cells | | target to VEGFR-3 |
| hsa-miR-1237-3p | 2587 | 3608 | esophageal cell line KYSE-150R | | |
| hsa-miR-1237-5p | 2588 | 3609 | esophageal cell line KYSE-150R | | |
| hsa-miR-1238-3p | 2589 | 3610 | | colorectal cancer | |
| hsa-miR-1238-5p | 2590 | 3611 | | colorectal cancer | |
| hsa-miR-1243 | 2591 | 3612 | discovered in embryonic stem cells | | |
| hsa-miR-124-3p | 2592 | 3613 | brain, plasma (exosomal) | glioma | cell differentiation |
| hsa-miR-1244 | 2593 | 3614 | discovered in embryonic stem cells | | |
| hsa-miR-1245a | 2594 | 3615 | discovered in embryonic stem cells | | |
| hsa-miR-1245b-3p | 2595 | 3616 | discovered in embryonic stem cells | | |
| hsa-miR-1245b-5p | 2596 | 3617 | discovered in embryonic stem cells | | |
| hsa-miR-124-5p | 2597 | 3618 | brain, Plasma (circulating) | upregulated in heart dysfunction, glioma | cell differentiation |
| hsa-miR-1246 | 2598 | 3619 | embryonic stem cells, epithelial cells | | |
| hsa-miR-1247-3p | 2599 | 3620 | embryoid body cells | | |
| hsa-miR-1247-5p | 2600 | 3621 | embryoid body cells | | |

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|---|---|---|---|---|---|
| hsa-miR-1248 | 2601 | 3622 | | | component of SnoRNAs |
| hsa-miR-1249 | 2602 | 3623 | liver(hepatocytes) | | |
| hsa-miR-1250 | 2603 | 3624 | oligodendrocytes | | |
| hsa-miR-1251 | 2604 | 3625 | discovered in embryonic stem cells | | |
| hsa-miR-1252 | 2605 | 3626 | discovered in embryonic stem cells | | |
| hsa-miR-1253 | 2606 | 3627 | discovered in embryonic stem cells | | |
| hsa-miR-1254 | 2607 | 3628 | embryonic stem cells | | |
| hsa-miR-1255a | 2608 | 3629 | discovered in embryonic stem cells | | |
| hsa-miR-1255b-2-3p | 2609 | 3630 | discovered in embryonic stem cells | | |
| hsa-miR-1255b-5p | 2610 | 3631 | discovered in embryonic stem cells | | |
| hsa-miR-1256 | 2611 | 3632 | discovered in embryonic stem cells | prostate cancer | |
| hsa-miR-1257 | 2612 | 3633 | discovered in embryonic stem cells | liposarcoma (soft tissue sarcoma) | |
| hsa-miR-1258 | 2613 | 3634 | discovered in embryonic stem cells | breast cancer and lung cancer | |
| hsa-miR-125a-3p | 2614 | 3635 | brain, hematopoietic cells | various cancer (prostate, HCC, etc) | cell proliferation and differentiation |
| hsa-miR-125a-5p | 2615 | 3636 | brain, hematopoietic cells | various cancer (prostate, HCC, etc) | cell proliferation and differentiation |
| hsa-miR-125b-1-3p | 2616 | 3637 | hematopoietic cells (monocytes), brain(neuron) | various cancer (prostate, HCC, etc) | oncogene, cell differentiation |
| hsa-miR-125b-2-3p | 2617 | 3638 | hematopoietic cells (monocytes), brain(neuron) | various cancer (prostate, HCC, etc) | oncogene, cell differentiation |
| hsa-miR-125b-5p | 2618 | 3639 | hematopoietic cells, brain (neuron) | various cancer (cutaneous T cell lymphoma, prostate, HCC, etc) | oncogene, cell differentiation |
| hsa-miR-1260a | 2619 | 3640 | periodontal tissue | | |
| hsa-miR-1260b | 2620 | 3641 | periodontal tissue | | |
| hsa-miR-1261 | 2621 | 3642 | embryonic stem cells | | |
| hsa-miR-1262 | 2622 | 3643 | embryoid body | | |

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|---|---|---|---|---|---|
| | | | cells | | |
| hsa-miR-1263 | 2623 | 3644 | discovered in embryonic stem cells | | |
| hsa-miR-126-3p | 2624 | 3645 | endothelial cells,lung | B-lieage ALL | angiogenesis |
| hsa-miR-1264 | 2625 | 3646 | discovered in embryonic stem cells | | |
| hsa-miR-1265 | 2626 | 3647 | discovered in embryonic stem cells | | |
| hsa-miR-126-5p | 2627 | 3648 | endothelial cells,lung | breast cancer, B-lieage ALL | angiogenesis |
| hsa-miR-1266 | 2628 | 3649 | embryonic stem cells | | |
| hsa-miR-1267 | 2629 | 3650 | discovered in embryonic stem cells | | |
| hsa-miR-1268a | 2630 | 3651 | embryonic stem cells | | |
| hsa-miR-1268b | 2631 | 3652 | embryonic stem cells | | |
| hsa-miR-1269a | 2632 | 3653 | embryoid body cells | | |
| hsa-miR-1269b | 2633 | 3654 | embryoid body cells | | |
| hsa-miR-1270 | 2634 | 3655 | discovered in embryonic stem cells | | |
| hsa-miR-1271-3p | 2635 | 3656 | brain | Hepatocellular carcinoma(HCC) | Suppress GPC-3 in HCC |
| hsa-miR-1271-5p | 2636 | 3657 | brain | Hepatocellular carcinoma(HCC) | Suppress GPC-3 in HCC |
| hsa-miR-1272 | 2637 | 3658 | embryonic stem cells | | |
| hsa-miR-1273a | 2638 | 3659 | discovered in embryonic stem cells | | |
| hsa-miR-1273c | 2639 | 3660 | | colorectal cancer | |
| hsa-miR-1273d | 2640 | 3661 | discovered in embryonic stem cells | | |
| hsa-miR-1273e | 2641 | 3662 | | solid tumor cells | |
| hsa-miR-1273f | 2642 | 3663 | | cervical cancer | |
| hsa-miR-1273g-3p | 2643 | 3664 | | cervical cancer | |
| hsa-miR-1273g-5p | 2644 | 3665 | | cervical cancer | |
| hsa-miR-127-3p | 2645 | 3666 | lung, placenta | | |
| hsa-miR-1275 | 2646 | 3667 | embryonic stem cells | gastric carcinoma | |
| hsa-miR-127-5p | 2647 | 3668 | lung, placenta(islet) | | |
| hsa-miR-1276 | 2648 | 3669 | discovered in embryonic stem cells | | |
| hsa-miR-1277-3p | 2649 | 3670 | embryoid body | | |

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|---|---|---|---|---|---|
| | | | cells | | |
| hsa-miR-1277-5p | 2650 | 3671 | embryoid body cells | | |
| hsa-miR-1278 | 2651 | 3672 | discovered in embryonic stem cells | | |
| hsa-miR-1279 | 2652 | 3673 | monocytes | | |
| hsa-miR-128 | 2653 | 3674 | glioblast, brain | B-lieage ALL | target to neurofibromin1in neuron |
| hsa-miR-1281 | 2654 | 3675 | | muscle invasive bladder cancer | |
| hsa-miR-1282 | 2655 | 3676 | discovered in embryonic stem cells | | |
| hsa-miR-1283 | 2656 | 3677 | placenta | | |
| hsa-miR-1284 | 2657 | 3678 | | lung cancer | |
| hsa-miR-1285-3p | 2658 | 3679 | | various cancer cells | inhibit P53 expression |
| hsa-miR-1285-5p | 2659 | 3680 | | various cancer cells | inhibit P53 expression |
| hsa-miR-1286 | 2660 | 3681 | smooth muscle | esophageal cancer | |
| hsa-miR-1287 | 2661 | 3682 | embryoid body cells | breast cancer | |
| hsa-miR-1288 | 2662 | 3683 | discovered in embryonic stem cells | | |
| hsa-miR-1289 | 2663 | 3684 | multiple cell types | | |
| hsa-miR-1290 | 2664 | 3685 | embryoid body cells | gastric carcinoma | |
| hsa-miR-1291 | 2665 | 3686 | hepatocytes | | component of SnoRNAs |
| hsa-miR-129-1-3p | 2666 | 3687 | multiple cell types | HCC cancer cells | |
| hsa-miR-1292-3p | 2667 | 3688 | | | |
| hsa-miR-129-2-3p | 2668 | 3689 | multiple cell types | various cancer cells | |
| hsa-miR-1292-5p | 2669 | 3690 | | | |
| hsa-miR-1293 | 2670 | 3691 | discovered in embryonic stem cells | | |
| hsa-miR-1294 | 2671 | 3692 | discovered in embryonic stem cells | | |
| hsa-miR-1295a | 2672 | 3693 | | tumor cells (follicular lymphoma) | |
| hsa-miR-1295b-3p | 2673 | 3694 | | tumor cells (follicular lymphoma) | |
| hsa-miR-1295b-5p | 2674 | 3695 | | tumor cells (follicular lymphoma) | |
| hsa-miR-129-5p | 2675 | 3696 | liver(hepatocytes) | HCC, thyroid cancer | cell death in cancer cell |
| hsa-miR-1296 | 2676 | 3697 | | breast cancer | |

| | | | | | |
|---|---|---|---|---|---|
| hsa-miR-1297 | 2677 | 3698 | discovered in embryonic stem cells | | |
| hsa-miR-1298 | 2678 | 3699 | | | |
| hsa-miR-1299 | 2679 | 3700 | discovered in embryonic stem cells | | |
| hsa-miR-1301 | 2680 | 3701 | | breast cancer | |
| hsa-miR-1302 | 2681 | 3702 | | | |
| hsa-miR-1303 | 2682 | 3703 | hepatocyte | colorectal cancer, liver cancer | |
| hsa-miR-1304-3p | 2683 | 3704 | | | dental development |
| hsa-miR-1304-5p | 2684 | 3705 | | | dental development |
| hsa-miR-1305 | 2685 | 3706 | discovered in embryonic stem cells | | |
| hsa-miR-1306-3p | 2686 | 3707 | discovered in embryonic stem cells | | |
| hsa-miR-1306-5p | 2687 | 3708 | discovered in embryonic stem cells | | |
| hsa-miR-1307-3p | 2688 | 3709 | discovered in embryonic stem cells | | |
| hsa-miR-1307-5p | 2689 | 3710 | discovered in embryonic stem cells | | |
| hsa-miR-130a-3p | 2690 | 3711 | lung, monocytes, vascular endothelial cells | various cancers (basal cell carcinoma, HCC,ovarian, etc), drug resistance | pro-angiogenic |
| hsa-miR-130a-5p | 2691 | 3712 | lung, monocytes, vascular endothelial cells | various cancers (basal cell carcinoma, HCC,ovarian, etc), drug resistance | pro-angiogenic |
| hsa-miR-130b-3p | 2692 | 3713 | Lung, epidermal cells( keratinocytes) | various cancers (gastric, rena cell carcinoma) | cell proiferation/sen escence |
| hsa-miR-130b-5p | 2693 | 3714 | Lung, epidermal cells( keratinocytes) | various cancers (gastric, rena cell carcinoma) | cell proiferation/sen escence |
| hsa-miR-1321 | 2694 | 3715 | | neuroblastoma | |
| hsa-miR-1322 | 2695 | 3716 | | neuroblastoma | |
| hsa-miR-1323 | 2696 | 3717 | placenta | neuroblastoma | |
| hsa-miR-132-3p | 2697 | 3718 | Brain(neuron), immune cells | | |
| hsa-miR-1324 | 2698 | 3719 | | neuroblastoma | |
| hsa-miR-132-5p | 2699 | 3720 | brain(neuron), | | |

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|---|---|---|---|---|---|
| | | | immune cells | | |
| hsa-miR-133a | 2700 | 3721 | muscle, heart, epithelial cells (lung) | heart failure, esophageal cancer | myogenesis |
| hsa-miR-133b | 2701 | 3722 | muscle, heart, epithelial cells (lung) | heart failure, esophageal cancer | myogenesis |
| hsa-miR-134 | 2702 | 3723 | lung (epithelial) | non-samll cell lung cancer, pulmonary embolism | |
| hsa-miR-1343 | 2703 | 3724 | | breast cancer cells | |
| hsa-miR-135a-3p | 2704 | 3725 | brain, other tissues | various cancer cells (lung, breast, colorectal, HCC, etc) | tumor suppressor |
| hsa-miR-135a-5p | 2705 | 3726 | brain, other tissues | various cancer cells (lung, breast, colorectal, HCC, etc) | tumor suppressor |
| hsa-miR-135b-3p | 2706 | 3727 | brain, placenta, other tissues | various cancers (gastric, mammary,neuroblastomas, pancreatic, etc) | |
| hsa-miR-135b-5p | 2707 | 3728 | brain, placenta, other tissues | various cancers (gastric, mammary,neuroblastomas, pancreatic, etc) | |
| hsa-miR-136-3p | 2708 | 3729 | stem cells, placenta | glioma | tumor suppressor |
| hsa-miR-136-5p | 2709 | 3730 | stem cells, placenta | glioma | tumor suppressor |
| hsa-miR-137 | 2710 | 3731 | brain | various cancers (glioblastoma, breast, gastric etc), Alzheimer's disease | inhibiting cancer cell proliferation and migration |
| hsa-miR-138-1-3p | 2711 | 3732 | stem cells, epidermal cells(keratinocytes) | arious cancer cells, downregulated in HCC | cell proliferation/senescence |
| hsa-miR-138-2-3p | 2712 | 3733 | stem cells | arious cancer cells, downregulated in HCC | |
| hsa-miR-138-5p | 2713 | 3734 | stem cells | arious cancer cells, downregulated in HCC | |
| hsa-miR-139-3p | 2714 | 3735 | hematocytes, brain | various cancer cells (colorectal, gastric, ovarian) | repress cancer metastasis |
| hsa-miR-139-5p | 2715 | 3736 | hematocytes, brain | various cancer | repress cancer |

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| | | | | cells (colorectal, gastric, ovarian) | metastasis |
| hsa-miR-140-3p | 2716 | 3737 | airway smooth muscle | Virus infection, cancers | |
| hsa-miR-140-5p | 2717 | 3738 | cartilage (chondrocytes) | csncers | |
| hsa-miR-141-3p | 2718 | 3739 | Many tissues/cells | various cancer cells (HCC, prostate, kidney, etc) | cell differentiation |
| hsa-miR-141-5p | 2719 | 3740 | Many tissues/cells | various cancer cells (HCC, prostate, kidney, etc) | cell differentiation |
| hsa-miR-142-3p | 2720 | 3741 | meyloid cells, hematopoiesis, APC cells | | immune response |
| hsa-miR-142-5p | 2721 | 3742 | meyloid cells, hematopoiesis, APC cells | | immune response |
| hsa-miR-143-3p | 2722 | 3743 | vascular smooth muscle | pre-B-cell acute lymphocytic leukemia , virus infection | |
| hsa-miR-143-5p | 2723 | 3744 | vascular smooth muscle, T-cells | virus infection | |
| hsa-miR-144-3p | 2724 | 3745 | erythroid | various cancers (lung, colorectal, etc) | cell differentiation |
| hsa-miR-144-5p | 2725 | 3746 | erythroid | various cancers (lung, colorectal, etc) | cell differentiation |
| hsa-miR-145-3p | 2726 | 3747 | kidney, cartilage, vascular smooth muscle | T-cell lupus | tumor suppressor |
| hsa-miR-145-5p | 2727 | 3748 | kidney, cartilage, vascular smooth muscle | T-cell lupus | tumor suppressor |
| hsa-miR-1468 | 2728 | 3749 | | lung cancer | |
| hsa-miR-1469 | 2729 | 3750 | | tumor cell(follicular lymphoma), rectal cancer | |
| hsa-miR-146a-3p | 2730 | 3751 | immune cells, hematopoiesis | various cancers, endotoxin tolerance | |
| hsa-miR-146a-5p | 2731 | 3752 | immune cells, hematopoiesis | various cancers, endotoxin tolerance | |
| hsa-miR-146b-3p | 2732 | 3753 | immune cells | various cancers | |
| hsa-miR-146b-5p | 2733 | 3754 | Embryonic stem cells | various cancers (glioma) | tumor invation, migration |
| hsa-miR-1470 | 2734 | 3755 | | | |
| hsa-miR-1471 | 2735 | 3756 | | tumor cell(follicular | |

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| | | | | lymphoma), rectal cancer | |
| hsa-miR-147a | 2736 | 3757 | Macrophage | inflammatory response | |
| hsa-miR-147b | 2737 | 3758 | Macrophage | inflammatory response | |
| hsa-miR-148a-3p | 2738 | 3759 | hematopoietic cells | CLL, T-lineage ALL | |
| hsa-miR-148a-5p | 2739 | 3760 | hematopoietic cells | CLL, T-lineage ALL | |
| hsa-miR-148b-3p | 2740 | 3761 | neuron | | |
| hsa-miR-148b-5p | 2741 | 3762 | neuron | | |
| hsa-miR-149-3p | 2742 | 3763 | heart, brain | various cancers (glioma, colorectal, gastric, etc) | |
| hsa-miR-149-5p | 2743 | 3764 | heart, brain | various cancers (glioma, colorectal, gastric, etc) | |
| hsa-miR-150-3p | 2744 | 3765 | hematopoietic cells (lymphoid) | circulating plasma (acute myeloid leukemia) | |
| hsa-miR-150-5p | 2745 | 3766 | hematopoietic cells (lymphoid) | circulating plasma (acute myeloid leukemia) | |
| hsa-miR-151a-3p | 2746 | 3767 | neuron, fetal liver | | |
| hsa-miR-151a-5p | 2747 | 3768 | neuron, fetal liver | | |
| hsa-miR-151b | 2748 | 3769 | immune cells (B-cells) | | |
| hsa-miR-152 | 2749 | 3770 | liver | | |
| hsa-miR-153 | 2750 | 3771 | brain | | |
| hsa-miR-1537 | 2751 | 3772 | | | |
| hsa-miR-1538 | 2752 | 3773 | blood | Cancer cells | |
| hsa-miR-1539 | 2753 | 3774 | esophageal cell line KYSE-150R | | |
| hsa-miR-154-3p | 2754 | 3775 | embryonic stem cells | | |
| hsa-miR-154-5p | 2755 | 3776 | embryonic stem cells | | |
| hsa-miR-155-3p | 2756 | 3777 | T/B cells, monocytes,breast | various cancers (CLL, B cell lymphoma, breast, lung, ovarian, cervical, colorectal, prostate) | |
| hsa-miR-155-5p | 2757 | 3778 | T/B cells, monocytes,breast | various cancers (CLL, B cell lymphoma, breast, lung, ovarian, cervical, colorectal, prostate) | |
| hsa-miR-1587 | 2758 | 3779 | identified in B-cells | | |

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| hsa-miR-15a-3p | 2759 | 3780 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-15a-5p | 2760 | 3781 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-15b-3p | 2761 | 3782 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-15b-5p | 2762 | 3783 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-16-1-3p | 2763 | 3784 | embryonic stem cells, blood, hematopoietic tissues (spleen) | | |
| hsa-miR-16-2-3p | 2764 | 3785 | blood, lymphocyte, hematopoietic tissues (spleen) | | |
| hsa-miR-16-5p | 2765 | 3786 | Many tissues, blood | | |
| hsa-miR-17-3p | 2766 | 3787 | embryonic stem cells, endothelial cells, | | tumor angiogenesis |
| hsa-miR-17-5p | 2767 | 3788 | endothelial cells, kidney, breast; | | tumor angiogenesis |
| hsa-miR-181a-2-3p | 2768 | 3789 | glioblast, stem cells | | |
| hsa-miR-181a-3p | 2769 | 3790 | glioblast, myeloid cells, Embryonic stem cells | | |
| hsa-miR-181a-5p | 2770 | 3791 | glioblast, myeloid cells, Embryonic stem cells | | |
| hsa-miR-181b-3p | 2771 | 3792 | glioblast, Embryonic stem cells , epidermal (keratinocytes) | | cell proiferation/sen escence |
| hsa-miR-181b-5p | 2772 | 3793 | glioblast, Embryonic stem cells , epidermal (keratinocytes) | | cell proiferation/sen escence |
| hsa-miR-181c-3p | 2773 | 3794 | brain, stem cells/progenitor | variou cance cells (gliobasltoma, basal cell carcinoma, prostate) | cell differentiation |
| hsa-miR-181c-5p | 2774 | 3795 | brain, stem cells/progenitor | variou cance cells (gliobasltoma, basal cell carcinoma, prostate) | cell differentiation |
| hsa-miR-181d | 2775 | 3796 | glia cells | | |
| hsa-miR-182-3p | 2776 | 3797 | immune cells | autoimmune | immune response |
| hsa-miR-1825 | 2777 | 3798 | discovered in a MiRDeep screening | | |

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|---|---|---|---|---|---|
| hsa-miR-182-5p | 2778 | 3799 | lung, immune cells | autoimmune | immune response |
| hsa-miR-1827 | 2779 | 3800 | | small cell lung cancer | |
| hsa-miR-183-3p | 2780 | 3801 | brain | | |
| hsa-miR-183-5p | 2781 | 3802 | brain | | |
| hsa-miR-184 | 2782 | 3803 | blood, tongue, pancreas (islet) | | |
| hsa-miR-185-3p | 2783 | 3804 | | | |
| hsa-miR-185-5p | 2784 | 3805 | | | |
| hsa-miR-186-3p | 2785 | 3806 | osteoblasts, heart | various cancer cells | |
| hsa-miR-186-5p | 2786 | 3807 | osteoblasts, heart | various cancer cells | |
| hsa-miR-187-3p | 2787 | 3808 | | thyroid tumor | |
| hsa-miR-187-5p | 2788 | 3809 | | thyroid tumor | |
| hsa-miR-188-3p | 2789 | 3810 | irway smooth muscle, central nervous system | | |
| hsa-miR-188-5p | 2790 | 3811 | irway smooth muscle, central nervous system | | |
| hsa-miR-18a-3p | 2791 | 3812 | endothelial cells, lung | | |
| hsa-miR-18a-5p | 2792 | 3813 | endothelial cells, lung | | |
| hsa-miR-18b-3p | 2793 | 3814 | lung | | |
| hsa-miR-18b-5p | 2794 | 3815 | lung | | |
| hsa-miR-1908 | 2795 | 3816 | | breast cancer | |
| hsa-miR-1909-3p | 2796 | 3817 | | rectal cancer | |
| hsa-miR-1909-5p | 2797 | 3818 | | rectal cancer | |
| hsa-miR-190a | 2798 | 3819 | brain | | |
| hsa-miR-190b | 2799 | 3820 | brain | | |
| hsa-miR-1910 | 2800 | 3821 | embryonic stem cells | | |
| hsa-miR-1911-3p | 2801 | 3822 | embryonic stem cells, neural precursor | | |
| hsa-miR-1911-5p | 2802 | 3823 | embryonic stem cells, neural precursor | | |
| hsa-miR-1912 | 2803 | 3824 | embryonic stem cells, neural precursor | | |
| hsa-miR-1913 | 2804 | 3825 | embryonic stem cells | | |
| hsa-miR-191-3p | 2805 | 3826 | | chroninc lymphocyte leukimia, B-lieage ALL | |
| hsa-miR-1914-3p | 2806 | 3827 | embryonic stem cells | | |
| hsa-miR-1914-5p | 2807 | 3828 | embryonic stem cells | | |

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| hsa-miR-1915-3p | 2808 | 3829 | embryonic stem cells | | |
| hsa-miR-1915-5p | 2809 | 3830 | embryonic stem cells | | |
| hsa-miR-191-5p | 2810 | 3831 | | chroninc lymphocyte leukimia, B-lieage ALL | |
| hsa-miR-192-3p | 2811 | 3832 | kidney | | |
| hsa-miR-192-5p | 2812 | 3833 | kidney | | |
| hsa-miR-193a-3p | 2813 | 3834 | many tissues/cells | various cancer cells (lung, osteoblastoma, ALL, follicular lymphoma, etc) | tumor suppressor, proliferation |
| hsa-miR-193a-5p | 2814 | 3835 | many tissues/cells | various cancer cells (lung, osteoblastoma, ALL, follicular lymphoma, etc) | tumor suppressor, proliferation |
| hsa-miR-193b-3p | 2815 | 3836 | many tissues/cells, semen | arious cancer cells (prostate, breast, melanoma, myeloma, non small cell lung, etc)follicular lymphoma) | tumor suppressor |
| hsa-miR-193b-5p | 2816 | 3837 | many tissues/cells, semen | arious cancer cells (prostate, breast, melanoma, myeloma, non small cell lung, etc)follicular lymphoma) | tumor suppressor |
| hsa-miR-194-3p | 2817 | 3838 | kidney,liver | various cancers | |
| hsa-miR-194-5p | 2818 | 3839 | kidney,liver | various cancers | |
| hsa-miR-195-3p | 2819 | 3840 | breast, pancreas (islet) | | |
| hsa-miR-195-5p | 2820 | 3841 | breast, pancreas (islet) | | |
| hsa-miR-196a-3p | 2821 | 3842 | pancreatic cells,endometrial tissues, mesenchymal stem cells | various cancer cells (pancreatic, osteosarcoma, endometrial, AML etc) | oncogenic, tumor suppressor |
| hsa-miR-196a-5p | 2822 | 3843 | pancreatic cells,endometrial tissues, mesenchymal stem cells | various cancer cells (pancreatic, osteosarcoma, endometrial, AML etc) | oncogenic, tumor suppressor |
| hsa-miR-196b-3p | 2823 | 3844 | endometrial tissues | glioblastoma | apoptosis |
| hsa-miR-196b-5p | 2824 | 3845 | endometrial tissues | glioblastoma | apoptosis |
| hsa-miR-1972 | 2825 | 3846 | | acute lymphoblastic leukemia | |

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| hsa-miR-1973 | 2826 | 3847 | | acute lymphoblastic leukemia | |
| hsa-miR-197-3p | 2827 | 3848 | blood (myeloid), other tissues/cells | various cancers (thyroid tumor, leukemia, etc) | |
| hsa-miR-197-5p | 2828 | 3849 | blood (myeloid), other tissues/cells | various cancers (thyroid tumor, leukemia, etc) | |
| hsa-miR-1976 | 2829 | 3850 | | acute lymphoblastic leukemia | |
| hsa-miR-198 | 2830 | 3851 | central nevous system(CNS) | | |
| hsa-miR-199a-3p | 2831 | 3852 | liver, embryoid body cells, cardiomyocytes | | |
| hsa-miR-199a-5p | 2832 | 3853 | liver, cardiomyocytes | | |
| hsa-miR-199b-3p | 2833 | 3854 | liver, osteoblast | various cancers | osteogenesis |
| hsa-miR-199b-5p | 2834 | 3855 | liver, osteoblast | various cancers | osteogenesis |
| hsa-miR-19a-3p | 2835 | 3856 | endothelial cells | | tumor angiogenesis |
| hsa-miR-19a-5p | 2836 | 3857 | endothelial cells | | tumor angiogenesis |
| hsa-miR-19b-1-5p | 2837 | 3858 | endothelial cells | | tumor angiogenesis |
| hsa-miR-19b-2-5p | 2838 | 3859 | endothelial cells | | tumor angiogenesis |
| hsa-miR-19b-3p | 2839 | 3860 | endothelial cells | | tumor angiogenesis |
| hsa-miR-200a-3p | 2840 | 3861 | epithelial cells, many other tissues | various cancers (breast, cervical, bladder, etc) | tumor progression and metastasis |
| hsa-miR-200a-5p | 2841 | 3862 | epithelial cells, many other tissues | various cancers (breast, cervical, bladder, etc) | tumor progression and metastasis |
| hsa-miR-200b-3p | 2842 | 3863 | epithelial cells, many other tissues | | tumor progression and metastasis |
| hsa-miR-200b-5p | 2843 | 3864 | epithelial cells, many other tissues | | tumor progression and metastasis |
| hsa-miR-200c-3p | 2844 | 3865 | epithelial cells, many other tissues, embryonic stem cells | | tumor progression and metastasis |
| hsa-miR-200c-5p | 2845 | 3866 | epithelial cells, many other tissues, embryonic stem cells | | tumor progression and metastasis |
| hsa-miR-202-3p | 2846 | 3867 | blood | lymphomagenesis, other cancers | |
| hsa-miR-202-5p | 2847 | 3868 | blood | lymphomagenesis, other cancers | |

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| hsa-miR-203a | 2848 | 3869 | skin (epithelium) | psoriasis, autoimmune | |
| hsa-miR-203b-3p | 2849 | 3870 | skin specific (epithelium) | psoriasis, autoimmune | |
| hsa-miR-203b-5p | 2850 | 3871 | skin specific (epithelium) | psoriasis, autoimmune | |
| hsa-miR-204-3p | 2851 | 3872 | adipose, other tissues/cells. kidney | various cancers | tumor metastasis |
| hsa-miR-204-5p | 2852 | 3873 | adipose, other tissues/cells, kidney | various cancers | tumor metastasis |
| hsa-miR-2052 | 2853 | 3874 | | | |
| hsa-miR-2053 | 2854 | 3875 | | | |
| hsa-miR-205-3p | 2855 | 3876 | blood(plasma) | various cancer cells (breast, glioma, melanoma, endometrial, etc) | |
| hsa-miR-2054 | 2856 | 3877 | | | |
| hsa-miR-205-5p | 2857 | 3878 | blood(plasma) | various cancer cells (breast, glioma, melanoma, endometrial, etc) | |
| hsa-miR-206 | 2858 | 3879 | muscle (cardiac and skeletal) | | myogenesis |
| hsa-miR-208a | 2859 | 3880 | heart(cardiomyocyte), muscle | cardiac defects | |
| hsa-miR-208b | 2860 | 3881 | heart(cardiomyocyte), muscle | cardiac defects | |
| hsa-miR-20a-3p | 2861 | 3882 | endothelial cells, kidney, osteogenic cells | | |
| hsa-miR-20a-5p | 2862 | 3883 | endothelial cells, kidney, osteogenic cells | | |
| hsa-miR-20b-3p | 2863 | 3884 | osteogenic cells | | |
| hsa-miR-20b-5p | 2864 | 3885 | osteogenic cells | | |
| hsa-miR-210 | 2865 | 3886 | kidney, heart, vascular endothelial cells | RCC, B-cell lymphocytes | angiogenesis |
| hsa-miR-2110 | 2866 | 3887 | | rectal cancer | |
| hsa-miR-2113 | 2867 | 3888 | embryonic stem cells | | |
| hsa-miR-211-3p | 2868 | 3889 | melanocytes | melanoma and other cancers | |
| hsa-miR-2114-3p | 2869 | 3890 | ovary, female reproductuve tract | | |
| hsa-miR-2114-5p | 2870 | 3891 | ovary, female reproductuve tract | | |
| hsa-miR-2115-3p | 2871 | 3892 | female reproductive tract | ovarian cancer | |
| hsa-miR-2115-5p | 2872 | 3893 | female reproductive tract | ovarian cancer | |
| hsa-miR-211-5p | 2873 | 3894 | melanocytes | melanoma and other cancers | |

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|---|---|---|---|---|---|
| hsa-miR-2116-3p | 2874 | 3895 | | live cancer(hepatocytes) and ovarian cancer | |
| hsa-miR-2116-5p | 2875 | 3896 | | live cancer(hepatocytes) and ovarian cancer | |
| hsa-miR-2117 | 2876 | 3897 | | ovarian cancer | |
| hsa-miR-212-3p | 2877 | 3898 | brain(neuron), spleen | lymphoma | |
| hsa-miR-212-5p | 2878 | 3899 | brain(neuron), spleen | lymphoma | |
| hsa-miR-21-3p | 2879 | 3900 | glioblast, Blood (meyloid cells), liver, vascular endothelial cells | autoimmune, heart diseases, cancers | |
| hsa-miR-214-3p | 2880 | 3901 | immune cerlls, pancreas | varioua cancers (melanoma, pancreatic, ovarian) | immune response |
| hsa-miR-214-5p | 2881 | 3902 | immune cells, pancreas | varioua cancers (melanoma, pancreatic, ovarian) | immune response |
| hsa-miR-215 | 2882 | 3903 | many tissues/cells | various cancers (renal, colon, osteosarcoma) | cell cycle arrest/p53 inducible |
| hsa-miR-21-5p | 2883 | 3904 | blood ( myeloid cells), liver, endothelial cells | autoimmune, heart diseases, cancers | |
| hsa-miR-216a-3p | 2884 | 3905 | kidney, pancreas | | |
| hsa-miR-216a-5p | 2885 | 3906 | kidney, pancreas | | |
| hsa-miR-216b | 2886 | 3907 | | cancers | senescence |
| hsa-miR-217 | 2887 | 3908 | endothelial cells | various cancer cells ( pancreas, kidney, breast) | |
| hsa-miR-218-1-3p | 2888 | 3909 | endothelial cells | various cancer cells (gastric tumor, bladder, cervical, etc) | |
| hsa-miR-218-2-3p | 2889 | 3910 | | various cancer cells (gastric tumor, bladder, cervical, etc) | |
| hsa-miR-218-5p | 2890 | 3911 | | various cancer cells (gastric tumor, bladder, cervical, etc) | |
| hsa-miR-219-1-3p | 2891 | 3912 | brain, oligodendrocytes | | |
| hsa-miR-219-2-3p | 2892 | 3913 | brain, oligodendrocytes | | |
| hsa-miR-219-5p | 2893 | 3914 | brain, oligodendrocytes | | |

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| hsa-miR-221-3p | 2894 | 3915 | endothelial cells, immune cells | leukemia and other cancers | angiogenesis/vasculogenesis |
| hsa-miR-221-5p | 2895 | 3916 | endothelial cells, immune cells | leukemia and other cancers | angiogenesis/vasculogenesis |
| hsa-miR-222-3p | 2896 | 3917 | endothelial cells | various cancers | angiogenesis |
| hsa-miR-222-5p | 2897 | 3918 | endothelial cells | various cancers | angiogenesis |
| hsa-miR-223-3p | 2898 | 3919 | meyloid cells | leukemia | |
| hsa-miR-223-5p | 2899 | 3920 | meyloid cells | leukemia | |
| hsa-miR-22-3p | 2900 | 3921 | many tissues/cells | various cancers | tumorigenesis |
| hsa-miR-224-3p | 2901 | 3922 | blood(plasma), ovary | cancers and inflammation | |
| hsa-miR-224-5p | 2902 | 3923 | blood(plasma), ovary | cancers and inflammation | |
| hsa-miR-22-5p | 2903 | 3924 | many tissues/cells | Various cancers | tumorigenesis |
| hsa-miR-2276 | 2904 | 3925 | | breast cancer | |
| hsa-miR-2277-3p | 2905 | 3926 | female reproductive tract | | |
| hsa-miR-2277-5p | 2906 | 3927 | female reproductive tract | | |
| hsa-miR-2278 | 2907 | 3928 | | breast cancer | |
| hsa-miR-2355-3p | 2908 | 3929 | embryonic stem cells | | |
| hsa-miR-2355-5p | 2909 | 3930 | embryonic stem cells | | |
| hsa-miR-2392 | 2910 | 3931 | identified in B-cells | | |
| hsa-miR-23a-3p | 2911 | 3932 | brain(astrocyte), endothelial cells, blood(erythroid) | Cancers | |
| hsa-miR-23a-5p | 2912 | 3933 | brain(astrocyte), endothelial cells, blood(erythroid) | cancers | |
| hsa-miR-23b-3p | 2913 | 3934 | blood, meyloid cells | cancers (renal cancer, glioblastoma, prostate, etc) and autoimmune | |
| hsa-miR-23b-5p | 2914 | 3935 | blood, meyloid cells | cancers(glioblastoma, prostate, etc) and autoimmune | |
| hsa-miR-23c | 2915 | 3936 | | cervical cancer | |
| hsa-miR-24-1-5p | 2916 | 3937 | lung, meyloid cells | | |
| hsa-miR-24-2-5p | 2917 | 3938 | lung, meyloid cells | | |
| hsa-miR-24-3p | 2918 | 3939 | lung, meyloid cells | | |
| hsa-miR-2467-3p | 2919 | 3940 | | breast cancer | |
| hsa-miR-2467-5p | 2920 | 3941 | | breast cancer | |
| hsa-miR-25-3p | 2921 | 3942 | embryonic stem cells, airway smooth muscle | | |
| hsa-miR-25-5p | 2922 | 3943 | embryonic stem cells, airway smooth muscle | | |
| hsa-miR-2681-3p | 2923 | 3944 | | breast cancer | |
| hsa-miR-2681-5p | 2924 | 3945 | | breast cancer | |
| hsa-miR-2682-3p | 2925 | 3946 | | | |

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|---|---|---|---|---|---|
| hsa-miR-2682-5p | 2926 | 3947 | | | |
| hsa-miR-26a-1-3p | 2927 | 3948 | embryonic stem cells, blood , other tissues | CLL and other cancers | cell cycle and differentiation |
| hsa-miR-26a-2-3p | 2928 | 3949 | blood , other tissues | CLL and other cancers | cell cycle and differentiation |
| hsa-miR-26a-5p | 2929 | 3950 | blood , other tissues | CLL and other cancers | cell cycle and differentiation |
| hsa-miR-26b-3p | 2930 | 3951 | hematopoietic cells | | |
| hsa-miR-26b-5p | 2931 | 3952 | hematopoietic cells | | |
| hsa-miR-27a-3p | 2932 | 3953 | meyloid cells | various cancer cells | |
| hsa-miR-27a-5p | 2933 | 3954 | meyloid cells | various cancer cells | |
| hsa-miR-27b-3p | 2934 | 3955 | meyloid cells, vascular endothelial cells | various cancer cells | pro-angiogenic |
| hsa-miR-27b-5p | 2935 | 3956 | meyloid cells, vascular endothelial cells | various cancer cells | pro-angiogenic |
| hsa-miR-28-3p | 2936 | 3957 | blood(immune cells) | B/T cell lymphoma | |
| hsa-miR-28-5p | 2937 | 3958 | blood(immune cells) | B/T cell lymphoma | |
| hsa-miR-2861 | 2938 | 3959 | osteoblasts | basal cell carcinoma | |
| hsa-miR-2909 | 2939 | 3960 | T-Lymphocytes | | |
| hsa-miR-296-3p | 2940 | 3961 | kidney, heart,lung, entothelial cells | | angiogenesis |
| hsa-miR-2964a-3p | 2941 | 3962 | | | |
| hsa-miR-2964a-5p | 2942 | 3963 | | | |
| hsa-miR-296-5p | 2943 | 3964 | lung, liver, endothelial cells | | angiogenesis |
| hsa-miR-297 | 2944 | 3965 | oocyte and prostate | | |
| hsa-miR-298 | 2945 | 3966 | | breast cancer | |
| hsa-miR-299-3p | 2946 | 3967 | | myeloid leukaemia, hepatoma, breast cancer | |
| hsa-miR-299-5p | 2947 | 3968 | | myeloid leukaemia, hepatoma, breast cancer | |
| hsa-miR-29a-3p | 2948 | 3969 | immuno system | CLL, other cancers, neurodegenative disease | tumor suppression, immune modulation |
| hsa-miR-29a-5p | 2949 | 3970 | immuno system | CLL, other cancers, neurodegenative disease | tumor suppression, immune modulation |
| hsa-miR-29b-1-5p | 2950 | 3971 | immuno system | CLL, other cancers, neurodegenative disease | tumor suppression, immune modulation |

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|---|---|---|---|---|---|
| hsa-miR-29b-2-5p | 2951 | 3972 | immuno system | CLL, other cancers | tumor suppression, immune modulation |
| hsa-miR-29b-3p | 2952 | 3973 | immuno system | CLL, other cancers | tumor suppression, immune modulation |
| hsa-miR-29c-3p | 2953 | 3974 | immuno system | CLL, other cancers | tumor suppression, immune modulation |
| hsa-miR-29c-5p | 2954 | 3975 | immuno system | CLL, other cancers | tumor suppression, immune modulation |
| hsa-miR-300 | 2955 | 3976 | osteoblast | Bladder cancer | |
| hsa-miR-301a-3p | 2956 | 3977 | embryonic stem cells | | |
| hsa-miR-301a-5p | 2957 | 3978 | embryonic stem cells | | |
| hsa-miR-301b | 2958 | 3979 | | esophageal adenocarcinoma, colonic cancer | |
| hsa-miR-302a-3p | 2959 | 3980 | embryonic stem cells, lipid metabolism | | lipid metabolism |
| hsa-miR-302a-5p | 2960 | 3981 | embryonic stem cells, lipid metabolism | | lipid metabolism |
| hsa-miR-302b-3p | 2961 | 3982 | embryonic stem cells | | |
| hsa-miR-302b-5p | 2962 | 3983 | embryonic stem cells | | |
| hsa-miR-302c-3p | 2963 | 3984 | embryonic stem cells | | |
| hsa-miR-302c-5p | 2964 | 3985 | embryonic stem cells | | |
| hsa-miR-302d-3p | 2965 | 3986 | embryonic stem cells | | |
| hsa-miR-302d-5p | 2966 | 3987 | embryonic stem cells | | |
| hsa-miR-302e | 2967 | 3988 | embryoid body cells | | |
| hsa-miR-302f | 2968 | 3989 | | gastric cancer | |
| hsa-miR-3064-3p | 2969 | 3990 | | | |
| hsa-miR-3064-5p | 2970 | 3991 | | | |
| hsa-miR-3065-3p | 2971 | 3992 | oligodendrocytes | anti-virus response | |
| hsa-miR-3065-5p | 2972 | 3993 | oligodendrocytes | solid tumors | |
| hsa-miR-3074-3p | 2973 | 3994 | | various cancer(melanoma, breast) | |
| hsa-miR-3074-5p | 2974 | 3995 | | various cancer(melanoma, | |

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|---|---|---|---|---|---|
| | | | | breast) | |
| hsa-miR-30a-3p | 2975 | 3996 | kidney, pancreatic cells | various cancers | autophagy |
| hsa-miR-30a-5p | 2976 | 3997 | CNS(prefrontal cortex), other tissues | glioma, colon carcinoma | autophagy |
| hsa-miR-30b-3p | 2977 | 3998 | kidney, adipose, CNS(prefrontal cortex) | | |
| hsa-miR-30b-5p | 2978 | 3999 | kidney, adipose, CNS(prefrontal cortex) | | |
| hsa-miR-30c-1-3p | 2979 | 4000 | kidney, adipose, CNS(prefrontal cortex) | | |
| hsa-miR-30c-2-3p | 2980 | 4001 | kidney, adipose, CNS(prefrontal cortex) | | |
| hsa-miR-30c-5p | 2981 | 4002 | kidney, adipose, CNS(prefrontal cortex) | | |
| hsa-miR-30d-3p | 2982 | 4003 | CNS (prefrontal cortex | | |
| hsa-miR-30d-5p | 2983 | 4004 | CNS (prefrontal cortex, embryoid body cells | | |
| hsa-miR-30e-3p | 2984 | 4005 | myeloid cells, glia cells | | |
| hsa-miR-30e-5p | 2985 | 4006 | myeloid cells, glia cells | | |
| hsa-miR-3115 | 2986 | 4007 | | various cancer (melanoma, breast tumor) | |
| hsa-miR-3116 | 2987 | 4008 | discovered in the melanoma miRNAome | | |
| hsa-miR-3117-3p | 2988 | 4009 | discovered in the melanoma miRNAome | | |
| hsa-miR-3117-5p | 2989 | 4010 | discovered in the melanoma miRNAome | | |
| hsa-miR-3118 | 2990 | 4011 | discovered in the melanoma miRNAome | | |
| hsa-miR-3119 | 2991 | 4012 | discovered in the melanoma miRNAome | | |
| hsa-miR-3120-3p | 2992 | 4013 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3120-5p | 2993 | 4014 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3121-3p | 2994 | 4015 | discovered in the | breast tumor | |

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|---|---|---|---|---|---|
| | | | melanoma miRNAome | | |
| hsa-miR-3121-5p | 2995 | 4016 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3122 | 2996 | 4017 | discovered in the melanoma miRNAome | | |
| hsa-miR-3123 | 2997 | 4018 | discovered in the melanoma miRNAome | | |
| hsa-miR-3124-3p | 2998 | 4019 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3124-5p | 2999 | 4020 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3125 | 3000 | 4021 | discovered in the melanoma miRNAome | | |
| hsa-miR-3126-3p | 3001 | 4022 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3126-5p | 3002 | 4023 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3127-3p | 3003 | 4024 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3127-5p | 3004 | 4025 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3128 | 3005 | 4026 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3129-3p | 3006 | 4027 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3129-5p | 3007 | 4028 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3130-3p | 3008 | 4029 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3130-5p | 3009 | 4030 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3131 | 3010 | 4031 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3132 | 3011 | 4032 | discovered in the melanoma miRNAome | | |
| hsa-miR-3133 | 3012 | 4033 | discovered in the melanoma | | |

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|---|---|---|---|---|---|
| | | | miRNAome | | |
| hsa-miR-3134 | 3013 | 4034 | discovered in the melanoma miRNAome | | |
| hsa-miR-3135a | 3014 | 4035 | discovered in the melanoma miRNAome | | |
| hsa-miR-3135b | 3015 | 4036 | discovered in B cells | | |
| hsa-miR-3136-3p | 3016 | 4037 | discovered in the melanoma miRNAome | lymphoblastic leukaemia and breast tumor | |
| hsa-miR-3136-5p | 3017 | 4038 | discovered in the melanoma miRNAome | lymphoblastic leukaemia and breast tumor | |
| hsa-miR-3137 | 3018 | 4039 | discovered in the melanoma miRNAome | | |
| hsa-miR-3138 | 3019 | 4040 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3139 | 3020 | 4041 | discovered in the melanoma miRNAome | | |
| hsa-miR-31-3p | 3021 | 4042 | | | |
| hsa-miR-3140-3p | 3022 | 4043 | discovered in the melanoma miRNAome, ovary | lymphoblastic leukaemia and breast tumor | |
| hsa-miR-3140-5p | 3023 | 4044 | discovered in the melanoma miRNAome, ovary | lymphoblastic leukaemia and breast tumor | |
| hsa-miR-3141 | 3024 | 4045 | discovered in the melanoma miRNAome | | |
| hsa-miR-3142 | 3025 | 4046 | discovered in the melanoma miRNAome; immune cells | | |
| hsa-miR-3143 | 3026 | 4047 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3144-3p | 3027 | 4048 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3144-5p | 3028 | 4049 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3145-3p | 3029 | 4050 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3145-5p | 3030 | 4051 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3146 | 3031 | 4052 | discovered in the melanoma | breast tumor | |

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| | | | miRNAome | | |
| hsa-miR-3147 | 3032 | 4053 | discovered in the melanoma miRNAome | | |
| hsa-miR-3148 | 3033 | 4054 | discovered in the melanoma miRNAome | | |
| hsa-miR-3149 | 3034 | 4055 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3150a-3p | 3035 | 4056 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3150a-5p | 3036 | 4057 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3150b-3p | 3037 | 4058 | discovered in the melanoma miRNAome | breast tumor and lymphoblastic leukaemia | |
| hsa-miR-3150b-5p | 3038 | 4059 | discovered in the melanoma miRNAome | breast tumor and lymphoblastic leukaemia | |
| hsa-miR-3151 | 3039 | 4060 | discovered in the melanoma miRNAome | lymphoblastic leukaemia | |
| hsa-miR-3152-3p | 3040 | 4061 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3152-5p | 3041 | 4062 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3153 | 3042 | 4063 | discovered in the melanoma miRNAome | | |
| hsa-miR-3154 | 3043 | 4064 | discovered in the melanoma miRNAome | lymphoblastic leukaemia | |
| hsa-miR-3155a | 3044 | 4065 | discovered in the melanoma miRNAome | | |
| hsa-miR-3155b | 3045 | 4066 | discovered in B cells | | |
| hsa-miR-3156-3p | 3046 | 4067 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3156-5p | 3047 | 4068 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3157-3p | 3048 | 4069 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3157-5p | 3049 | 4070 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3158-3p | 3050 | 4071 | discovered in the | breast tumor | |

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| | | | melanoma miRNAome, ovary | | |
| hsa-miR-3158-5p | 3051 | 4072 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3159 | 3052 | 4073 | discovered in the melanoma miRNAome | | |
| hsa-miR-31-5p | 3053 | 4074 | | various cancer cells (breast, lung, prostate) | |
| hsa-miR-3160-3p | 3054 | 4075 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3160-5p | 3055 | 4076 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3161 | 3056 | 4077 | discovered in the melanoma miRNAome | | |
| hsa-miR-3162-3p | 3057 | 4078 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3162-5p | 3058 | 4079 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3163 | 3059 | 4080 | discovered in the melanoma miRNAome | | |
| hsa-miR-3164 | 3060 | 4081 | discovered in the melanoma miRNAome | | |
| hsa-miR-3165 | 3061 | 4082 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3166 | 3062 | 4083 | discovered in the melanoma miRNAome | | |
| hsa-miR-3167 | 3063 | 4084 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3168 | 3064 | 4085 | discovered in the melanoma miRNAome | | |
| hsa-miR-3169 | 3065 | 4086 | discovered in the melanoma miRNAome | | |
| hsa-miR-3170 | 3066 | 4087 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3171 | 3067 | 4088 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3173-3p | 3068 | 4089 | discovered in the melanoma | breast tumor | |

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| | | | miRNAome | | |
| hsa-miR-3173-5p | 3069 | 4090 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3174 | 3070 | 4091 | discovered in the melanoma miRNAome | | |
| hsa-miR-3175 | 3071 | 4092 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3176 | 3072 | 4093 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3177-3p | 3073 | 4094 | discovered in the melanoma miRNAome | breast tumor and lymphoblastic leukaemia | |
| hsa-miR-3177-5p | 3074 | 4095 | discovered in the melanoma miRNAome | breast tumor and lymphoblastic leukaemia | |
| hsa-miR-3178 | 3075 | 4096 | discovered in the melanoma miRNAome | | |
| hsa-miR-3179 | 3076 | 4097 | discovered in the melanoma miRNAome | | |
| hsa-miR-3180 | 3077 | 4098 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3180-3p | 3078 | 4099 | discovered in breast tunor | | |
| hsa-miR-3180-5p | 3079 | 4100 | discovered in breast tumor | | |
| hsa-miR-3181 | 3080 | 4101 | discovered in the melanoma miRNAome | | |
| hsa-miR-3182 | 3081 | 4102 | discovered in the melanoma miRNAome | | |
| hsa-miR-3183 | 3082 | 4103 | discovered in the melanoma miRNAome | | |
| hsa-miR-3184-3p | 3083 | 4104 | discovered in the melanoma miRNAome | | |
| hsa-miR-3184-5p | 3084 | 4105 | discovered in the melanoma miRNAome | | |
| hsa-miR-3185 | 3085 | 4106 | discovered in the melanoma miRNAome | | |
| hsa-miR-3186-3p | 3086 | 4107 | discovered in the melanoma miRNAome, ovary | | |
| hsa-miR-3186-5p | 3087 | 4108 | discovered in the melanoma | | |

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| | | | miRNAome, ovary | | |
| hsa-miR-3187-3p | 3088 | 4109 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3187-5p | 3089 | 4110 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3188 | 3090 | 4111 | discovered in the melanoma miRNAome | | |
| hsa-miR-3189-3p | 3091 | 4112 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3189-5p | 3092 | 4113 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3190-3p | 3093 | 4114 | discovered in the melanoma miRNAome | lymphoblastic leukaemia | |
| hsa-miR-3190-5p | 3094 | 4115 | discovered in the melanoma miRNAome | lymphoblastic leukaemia | |
| hsa-miR-3191-3p | 3095 | 4116 | discovered in the melanoma miRNAome | | |
| hsa-miR-3191-5p | 3096 | 4117 | discovered in the melanoma miRNAome | | |
| hsa-miR-3192 | 3097 | 4118 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3193 | 3098 | 4119 | discovered in the melanoma miRNAome | | |
| hsa-miR-3194-3p | 3099 | 4120 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3194-5p | 3100 | 4121 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3195 | 3101 | 4122 | discovered in the melanoma miRNAome | | |
| hsa-miR-3196 | 3102 | 4123 | | basal cell carcinoma | |
| hsa-miR-3197 | 3103 | 4124 | discovered in the melanoma miRNAome | | |
| hsa-miR-3198 | 3104 | 4125 | discovered in the melanoma miRNAome | breast tumor | |
| hsa-miR-3199 | 3105 | 4126 | discovered in the melanoma miRNAome | | |
| hsa-miR-3200-3p | 3106 | 4127 | discovered in the | breast tumor | |

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| | | | melanoma miRNAome, ovary | | |
| hsa-miR-3200-5p | 3107 | 4128 | discovered in the melanoma miRNAome, ovary | breast tumor | |
| hsa-miR-3201 | 3108 | 4129 | discovered in the melanoma miRNAome, | | |
| hsa-miR-3202 | 3109 | 4130 | discovered in the melanoma miRNAome,epithelial cell BEAS2B | | |
| hsa-miR-320a | 3110 | 4131 | blood, heart(myocardiac) | colon cancer cells, heart disease | |
| hsa-miR-320b | 3111 | 4132 | central nevous system | | |
| hsa-miR-320c | 3112 | 4133 | chondrocyte | | cartilage metabolism |
| hsa-miR-320d | 3113 | 4134 | | cancer stem cells | |
| hsa-miR-320e | 3114 | 4135 | neural cells | | |
| hsa-miR-323a-3p | 3115 | 4136 | neurons | myeloid leukaemia, mudulla thyroid carcinoma | |
| hsa-miR-323a-5p | 3116 | 4137 | neurons | myeloid leukaemia, mudulla thyroid carcinoma | |
| hsa-miR-323b-3p | 3117 | 4138 | | myeloid leukaemia | |
| hsa-miR-323b-5p | 3118 | 4139 | | myeloid leukaemia | |
| hsa-miR-32-3p | 3119 | 4140 | blood, glia | various cancers (lung, kidney, prostate, etc), virus infection | |
| hsa-miR-324-3p | 3120 | 4141 | kidney | | |
| hsa-miR-324-5p | 3121 | 4142 | neurons | tumor cells | |
| hsa-miR-325 | 3122 | 4143 | neurons, placenta | | |
| hsa-miR-32-5p | 3123 | 4144 | blood, glia | various cancers (lung, kidney, prostate, etc), virus infection | |
| hsa-miR-326 | 3124 | 4145 | neurons | tumor cells | |
| hsa-miR-328 | 3125 | 4146 | neuron, blood | tumor cells | |
| hsa-miR-329 | 3126 | 4147 | brain and platele | | |
| hsa-miR-330-3p | 3127 | 4148 | | various cancers( prostate, glioblastoma, colorectal) | |
| hsa-miR-330-5p | 3128 | 4149 | | various cancers( prostate, glioblastoma, colorectal) | |

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|---|---|---|---|---|---|
| hsa-miR-331-3p | 3129 | 4150 | | gastric cancer | |
| hsa-miR-331-5p | 3130 | 4151 | lymphocytes | | |
| hsa-miR-335-3p | 3131 | 4152 | kidney, breast | RCC, multiple myeloma | |
| hsa-miR-335-5p | 3132 | 4153 | kidney, breast | RCC, multiple myeloma | |
| hsa-miR-337-3p | 3133 | 4154 | lung | gastric cancer | |
| hsa-miR-337-5p | 3134 | 4155 | lung | | |
| hsa-miR-338-3p | 3135 | 4156 | epithelial cells, oligodendrocytes | gastric, rectal cancer cells, osteosarcoma | |
| hsa-miR-338-5p | 3136 | 4157 | oligodendrocytes | gastric cancer | |
| hsa-miR-339-3p | 3137 | 4158 | immune cell | | |
| hsa-miR-339-5p | 3138 | 4159 | immune cell | | |
| hsa-miR-33a-3p | 3139 | 4160 | pancreatic islet, lipid metabolism | | lipid metabolism |
| hsa-miR-33a-5p | 3140 | 4161 | pancreatic islet, lipid metabolism | | lipid metabolism |
| hsa-miR-33b-3p | 3141 | 4162 | lipid metabolism | | lipid metabolism |
| hsa-miR-33b-5p | 3142 | 4163 | lipid metabolism | | lipid metabolism |
| hsa-miR-340-3p | 3143 | 4164 | | various cancers | |
| hsa-miR-340-5p | 3144 | 4165 | embryoid body cells | | |
| hsa-miR-342-3p | 3145 | 4166 | brain, circulating plasma | multiple myeloma, other cancers | |
| hsa-miR-342-5p | 3146 | 4167 | circulating plasma | multiple myeloma, other cancers | |
| hsa-miR-345-3p | 3147 | 4168 | hematopoietic cells | follicular lymphoma, other cancers | |
| hsa-miR-345-5p | 3148 | 4169 | hematopoietic cells | follicular lymphoma, other cancers | |
| hsa-miR-346 | 3149 | 4170 | immume cells | cancers and autoimmune | |
| hsa-miR-34a-3p | 3150 | 4171 | breast, meyloid cells, ciliated epithelial cells | gastric cancer, CLL, other | tumor suppressor, p53 inducible |
| hsa-miR-34a-5p | 3151 | 4172 | breast, meyloid cells, ciliated epithelial cells | gastric cancer, CLL, other | tumor suppressor, p53 inducible |
| hsa-miR-34b-3p | 3152 | 4173 | ciliated epithelial cells | various cancers | tumor suppressor, p53 inducible |
| hsa-miR-34b-5p | 3153 | 4174 | ciliated epithelial cells | various cancers | tumor suppressor, p53 inducible |
| hsa-miR-34c-3p | 3154 | 4175 | ciliated epithelial cells, placenta | various cancers | tumor suppressor, p53 inducible |
| hsa-miR-34c-5p | 3155 | 4176 | ciliated epithelial | various cancers | tumor |

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| | | | cells, placenta | | suppressor, p53 inducible |
| hsa-miR-3529-3p | 3156 | 4177 | discovered in breast tumor | | |
| hsa-miR-3529-5p | 3157 | 4178 | discovered in breast tumor | | |
| hsa-miR-3591-3p | 3158 | 4179 | discovered in breast tumor | | |
| hsa-miR-3591-5p | 3159 | 4180 | discovered in breast tumor | | |
| hsa-miR-3605-3p | 3160 | 4181 | discovered in reprodcutive tracts | | |
| hsa-miR-3605-5p | 3161 | 4182 | discovered in reprodcutive tracts | | |
| hsa-miR-3606-3p | 3162 | 4183 | discovered in cervical tumors | | |
| hsa-miR-3606-5p | 3163 | 4184 | discovered in cervical tumors | | |
| hsa-miR-3607-3p | 3164 | 4185 | discovered in cervical tumors | | |
| hsa-miR-3607-5p | 3165 | 4186 | discovered in cervical tumors | | |
| hsa-miR-3609 | 3166 | 4187 | discovered in cervical tumors | | |
| hsa-miR-3610 | 3167 | 4188 | discovered in cervical tumors | | |
| hsa-miR-3611 | 3168 | 4189 | discovered in cervical tumors | | |
| hsa-miR-3612 | 3169 | 4190 | discovered in cervical tumors | | |
| hsa-miR-3613-3p | 3170 | 4191 | discovered in cervical tumors | | |
| hsa-miR-3613-5p | 3171 | 4192 | discovered in cervical tumors | | |
| hsa-miR-361-3p | 3172 | 4193 | blood, endothelial cells | | |
| hsa-miR-3614-3p | 3173 | 4194 | discovered in cervical and breast tumors | | |
| hsa-miR-3614-5p | 3174 | 4195 | discovered in cervical and breast tumors | | |
| hsa-miR-3615 | 3175 | 4196 | discovered in cervical tumors | | |
| hsa-miR-361-5p | 3176 | 4197 | endothelial cells | | |
| hsa-miR-3616-3p | 3177 | 4198 | discovered in cervical tumors | | |
| hsa-miR-3616-5p | 3178 | 4199 | discovered in cervical tumors | | |
| hsa-miR-3617-3p | 3179 | 4200 | discovered in cervical tumors and psoriasis | | |
| hsa-miR-3617-5p | 3180 | 4201 | discovered in cervical tumors and psoriasis | | |

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|---|---|---|---|---|---|
| hsa-miR-3618 | 3181 | 4202 | discovered in cervical tumors | | |
| hsa-miR-3619-3p | 3182 | 4203 | discovered in breast tumors | | |
| hsa-miR-3619-5p | 3183 | 4204 | discovered in breast tumors | | |
| hsa-miR-3620-3p | 3184 | 4205 | discovered in cervical tumors | | |
| hsa-miR-3620-5p | 3185 | 4206 | discovered in cervical tumors | | |
| hsa-miR-3621 | 3186 | 4207 | discovered in cervical tumors | | |
| hsa-miR-3622a-3p | 3187 | 4208 | discovered in breast tumors | | |
| hsa-miR-3622a-5p | 3188 | 4209 | discovered in breast tumors | | |
| hsa-miR-3622b-3p | 3189 | 4210 | discovered in cervical tumors | | |
| hsa-miR-3622b-5p | 3190 | 4211 | discovered in cervical tumors | | |
| hsa-miR-362-3p | 3191 | 4212 | | melanoma | |
| hsa-miR-362-5p | 3192 | 4213 | | melanoma | |
| hsa-miR-363-3p | 3193 | 4214 | kidney stem cell, blood cells | | |
| hsa-miR-363-5p | 3194 | 4215 | kidney stem cell, blood cells | | |
| hsa-miR-3646 | 3195 | 4216 | discovered in solid tumor | | |
| hsa-miR-3648 | 3196 | 4217 | discovered in solid tumor | | |
| hsa-miR-3649 | 3197 | 4218 | discovered in solid tumor | | |
| hsa-miR-3650 | 3198 | 4219 | discovered in solid tumor | | |
| hsa-miR-3651 | 3199 | 4220 | discovered in solid tumor | | |
| hsa-miR-3652 | 3200 | 4221 | discovered in solid tumor | | |
| hsa-miR-3653 | 3201 | 4222 | discovered in solid tumor | | |
| hsa-miR-3654 | 3202 | 4223 | discovered in solid tumor | | |
| hsa-miR-3655 | 3203 | 4224 | discovered in solid tumor | | |
| hsa-miR-3656 | 3204 | 4225 | discovered in solid tumor | | |
| hsa-miR-3657 | 3205 | 4226 | discovered in solid tumor | | |
| hsa-miR-3658 | 3206 | 4227 | discovered in solid tumor | | |
| hsa-miR-3659 | 3207 | 4228 | discovered in breast tumors | | |
| hsa-miR-365a-3p | 3208 | 4229 | | various cancer cells (Immune cells, lung, colon, | apoptosis |

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|---|---|---|---|---|---|
| | | | | endometriotic) | |
| hsa-miR-365a-5p | 3209 | 4230 | | various cancer cells (Immune cells, lung, colon, endometriotic)) | apoptosis |
| hsa-miR-365b-3p | 3210 | 4231 | | various cancers (retinoblastoma,colon, endometriotic) | apoptosis |
| hsa-miR-365b-5p | 3211 | 4232 | | various cancers (colon, endometriotic) | apoptosis |
| hsa-miR-3660 | 3212 | 4233 | discovered in breast tumors | | |
| hsa-miR-3661 | 3213 | 4234 | discovered in breast tumors | | |
| hsa-miR-3662 | 3214 | 4235 | | | |
| hsa-miR-3663-3p | 3215 | 4236 | | | |
| hsa-miR-3663-5p | 3216 | 4237 | | | |
| hsa-miR-3664-3p | 3217 | 4238 | discovered in breast tumors | | |
| hsa-miR-3664-5p | 3218 | 4239 | discovered in breast tumors | | |
| hsa-miR-3665 | 3219 | 4240 | brain | | |
| hsa-miR-3666 | 3220 | 4241 | brain | | |
| hsa-miR-3667-3p | 3221 | 4242 | discovered in peripheral blood | | |
| hsa-miR-3667-5p | 3222 | 4243 | discovered in peripheral blood | | |
| hsa-miR-3668 | 3223 | 4244 | discovered in peripheral blood | | |
| hsa-miR-3669 | 3224 | 4245 | discovered in peripheral blood | | |
| hsa-miR-3670 | 3225 | 4246 | discovered in peripheral blood | | |
| hsa-miR-3671 | 3226 | 4247 | discovered in peripheral blood | | |
| hsa-miR-3672 | 3227 | 4248 | discovered in peripheral blood | | |
| hsa-miR-3673 | 3228 | 4249 | discovered in peripheral blood | | |
| hsa-miR-367-3p | 3229 | 4250 | embryonic stem cells | | reprogramming |
| hsa-miR-3674 | 3230 | 4251 | discovered in peripheral blood | | |
| hsa-miR-3675-3p | 3231 | 4252 | discovered in peripheral blood | | |
| hsa-miR-3675-5p | 3232 | 4253 | discovered in peripheral blood | | |
| hsa-miR-367-5p | 3233 | 4254 | embryonic stem cells | | reprogramming |
| hsa-miR-3676-3p | 3234 | 4255 | discovered in peripheral blood | | |
| hsa-miR-3676-5p | 3235 | 4256 | discovered in peripheral blood | | |

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|---|---|---|---|---|---|
| hsa-miR-3677-3p | 3236 | 4257 | discovered in peripheral blood | | |
| hsa-miR-3677-5p | 3237 | 4258 | discovered in peripheral blood | | |
| hsa-miR-3678-3p | 3238 | 4259 | discovered in peripheral blood | | |
| hsa-miR-3678-5p | 3239 | 4260 | discovered in peripheral blood | | |
| hsa-miR-3679-3p | 3240 | 4261 | discovered in peripheral blood | | |
| hsa-miR-3679-5p | 3241 | 4262 | discovered in peripheral blood | | |
| hsa-miR-3680-3p | 3242 | 4263 | discovered in peripheral blood | | |
| hsa-miR-3680-5p | 3243 | 4264 | discovered in peripheral blood | | |
| hsa-miR-3681-3p | 3244 | 4265 | discovered in peripheral blood | | |
| hsa-miR-3681-5p | 3245 | 4266 | discovered in peripheral blood | | |
| hsa-miR-3682-3p | 3246 | 4267 | discovered in peripheral blood | | |
| hsa-miR-3682-5p | 3247 | 4268 | discovered in peripheral blood | | |
| hsa-miR-3683 | 3248 | 4269 | discovered in peripheral blood | | |
| hsa-miR-3684 | 3249 | 4270 | discovered in peripheral blood | | |
| hsa-miR-3685 | 3250 | 4271 | discovered in peripheral blood | | |
| hsa-miR-3686 | 3251 | 4272 | discovered in peripheral blood | | |
| hsa-miR-3687 | 3252 | 4273 | discovered in peripheral blood | | |
| hsa-miR-3688-3p | 3253 | 4274 | discovered in breast tumor | | |
| hsa-miR-3688-5p | 3254 | 4275 | discovered in breast tumor | | |
| hsa-miR-3689a-3p | 3255 | 4276 | discovered in female reproductuve tract | | |
| hsa-miR-3689a-5p | 3256 | 4277 | discovered in female reproductuve tract and peripheral blood | | |
| hsa-miR-3689b-3p | 3257 | 4278 | discovered in female reproductuve tract and peripheral blood | | |
| hsa-miR-3689b-5p | 3258 | 4279 | discovered in female reproductuve tract | | |
| hsa-miR-3689c | 3259 | 4280 | discovered in B | | |

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|---|---|---|---|---|---|
| | | | cells | | |
| hsa-miR-3689d | 3260 | 4281 | discovered in B cells | | |
| hsa-miR-3689e | 3261 | 4282 | discovered in B cells | | |
| hsa-miR-3689f | 3262 | 4283 | discovered in B cells | | |
| hsa-miR-3690 | 3263 | 4284 | discovered in peripheral blood | | |
| hsa-miR-3691-3p | 3264 | 4285 | discovered in peripheral blood | | |
| hsa-miR-3691-5p | 3265 | 4286 | discovered in peripheral blood | | |
| hsa-miR-3692-3p | 3266 | 4287 | discovered in peripheral blood | | |
| hsa-miR-3692-5p | 3267 | 4288 | discovered in peripheral blood | | |
| hsa-miR-369-3p | 3268 | 4289 | stem cells | | reprogramming |
| hsa-miR-369-5p | 3269 | 4290 | stem cells | | reprogramming |
| hsa-miR-370 | 3270 | 4291 | | acute meyloid leukaemia and other cancers | tumor suppressor, lipid metabolism |
| hsa-miR-3713 | 3271 | 4292 | discovered in neuroblastoma | | |
| hsa-miR-3714 | 3272 | 4293 | discovered in neuroblastoma | | |
| hsa-miR-371a-3p | 3273 | 4294 | serum | | |
| hsa-miR-371a-5p | 3274 | 4295 | serum | | |
| hsa-miR-371b-3p | 3275 | 4296 | serum | | |
| hsa-miR-371b-5p | 3276 | 4297 | serum | | |
| hsa-miR-372 | 3277 | 4298 | hematopoietic cells, lung, placental (blood) | | |
| hsa-miR-373-3p | 3278 | 4299 | | breast cancer | |
| hsa-miR-373-5p | 3279 | 4300 | | breast cancer | |
| hsa-miR-374a-3p | 3280 | 4301 | muscle (myoblasts) | breast and lung cancer | myogenic differentiation |
| hsa-miR-374a-5p | 3281 | 4302 | muscle (myoblasts) | breast and lung cancer | myogenic differentiation |
| hsa-miR-374b-3p | 3282 | 4303 | muscle (myoblasts) | | myogenic differentiation |
| hsa-miR-374b-5p | 3283 | 4304 | muscle (myoblasts) | | myogenic differentiation |
| hsa-miR-374c-3p | 3284 | 4305 | muscle (myoblasts) | | myogenic differentiation |
| hsa-miR-374c-5p | 3285 | 4306 | muscle (myoblasts) | | myogenic differentiation |
| hsa-miR-375 | 3286 | 4307 | pancreas (islet) | | |
| hsa-miR-376a-2-5p | 3287 | 4308 | regulatory miRs for hematopoietic cells (erythroid,platelet, lympho) | | |
| hsa-miR-376a-3p | 3288 | 4309 | regulatory miRs for hematopoietic cells (erythroid,platelet, | | |

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|---|---|---|---|---|---|
| | | | lympho) | | |
| hsa-miR-376a-5p | 3289 | 4310 | regulatory miRs for hematopoietic cells (erythroid,platelet, lympho) | | |
| hsa-miR-376b-3p | 3290 | 4311 | blood | various cancer cells | autophagy |
| hsa-miR-376b-5p | 3291 | 4312 | blood | various cancer cells | autophagy |
| hsa-miR-376c-3p | 3292 | 4313 | trophoblast | various cancer cells | cell proliferatio |
| hsa-miR-376c-5p | 3293 | 4314 | trophoblast | various cancer cells | cell proliferatio |
| hsa-miR-377-3p | 3294 | 4315 | hematopoietic cells | | |
| hsa-miR-377-5p | 3295 | 4316 | hematopoietic cells | | |
| hsa-miR-378a-3p | 3296 | 4317 | ovary, lipid metabolism | | |
| hsa-miR-378a-5p | 3297 | 4318 | ovary, placenta/trophoblast, lipid metabolism | | |
| hsa-miR-378b | 3298 | 4319 | lipid metabolism | | |
| hsa-miR-378c | 3299 | 4320 | lipid metabolism | | |
| hsa-miR-378d | 3300 | 4321 | lipid metabolism | | |
| hsa-miR-378e | 3301 | 4322 | lipid metabolism | | |
| hsa-miR-378f | 3302 | 4323 | lipid metabolism | | |
| hsa-miR-378g | 3303 | 4324 | lipid metabolism | | |
| hsa-miR-378h | 3304 | 4325 | lipid metabolism | | |
| hsa-miR-378i | 3305 | 4326 | lipid metabolism | | |
| hsa-miR-378j | 3306 | 4327 | lipid metabolism | | |
| hsa-miR-379-3p | 3307 | 4328 | | various cancers (breast, hepatocytes, colon) | |
| hsa-miR-379-5p | 3308 | 4329 | | various cancers (breast, hepatocytes, colon) | |
| hsa-miR-380-3p | 3309 | 4330 | brain | neuroblastoma | |
| hsa-miR-380-5p | 3310 | 4331 | brain, embryonic stem cells | neuroblastoma | |
| hsa-miR-381-3p | 3311 | 4332 | chondrogenesis, lung, brain | | |
| hsa-miR-381-5p | 3312 | 4333 | chondrogenesis, lung, brain | | |
| hsa-miR-382-3p | 3313 | 4334 | renal epithelial cells | | |
| hsa-miR-382-5p | 3314 | 4335 | renal epithelial cells | | |
| hsa-miR-383 | 3315 | 4336 | testes, brain (medulla) | | |
| hsa-miR-384 | 3316 | 4337 | epithelial cells | | |
| hsa-miR-3907 | 3317 | 4338 | discovered in female reproductive tract | | |
| hsa-miR-3908 | 3318 | 4339 | discovered in female reproductive | | |

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|---|---|---|---|---|---|
| | | | tract | | |
| hsa-miR-3909 | 3319 | 4340 | discovered in female reproductive tract | | |
| hsa-miR-3910 | 3320 | 4341 | discovered in female reproductive tract | | |
| hsa-miR-3911 | 3321 | 4342 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3912 | 3322 | 4343 | discovered in female reproductive tract | | |
| hsa-miR-3913-3p | 3323 | 4344 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3913-5p | 3324 | 4345 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3914 | 3325 | 4346 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3915 | 3326 | 4347 | discovered in female reproductive tract | | |
| hsa-miR-3916 | 3327 | 4348 | discovered in female reproductive tract | | |
| hsa-miR-3917 | 3328 | 4349 | discovered in female reproductive tract | | |
| hsa-miR-3918 | 3329 | 4350 | discovered in female reproductive tract | | |
| hsa-miR-3919 | 3330 | 4351 | discovered in female reproductive tract | | |
| hsa-miR-3920 | 3331 | 4352 | discovered in female reproductive tract | | |
| hsa-miR-3921 | 3332 | 4353 | discovered in female reproductive tract | | |
| hsa-miR-3922-3p | 3333 | 4354 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3922-5p | 3334 | 4355 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3923 | 3335 | 4356 | discovered in female reproductive tract | | |
| hsa-miR-3924 | 3336 | 4357 | discovered in female reproductive tract | | |

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| hsa-miR-3925-3p | 3337 | 4358 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3925-5p | 3338 | 4359 | discovered in breast tumor and female reproductive tract | | |
| hsa-miR-3926 | 3339 | 4360 | discovered in female reproductive tract | | |
| hsa-miR-3927-3p | 3340 | 4361 | discovered in female reproductive tract and psoriasis | | |
| hsa-miR-3927-5p | 3341 | 4362 | discovered in female reproductive tract and psoriasis | | |
| hsa-miR-3928 | 3342 | 4363 | discovered in female reproductive tract | | |
| hsa-miR-3929 | 3343 | 4364 | discovered in female reproductive tract | | |
| hsa-miR-3934-3p | 3344 | 4365 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-3934-5p | 3345 | 4366 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-3935 | 3346 | 4367 | | | |
| hsa-miR-3936 | 3347 | 4368 | discovered in breast tumor and lymphoblastic leukaemia | | |
| hsa-miR-3937 | 3348 | 4369 | | | |
| hsa-miR-3938 | 3349 | 4370 | | | |
| hsa-miR-3939 | 3350 | 4371 | | | |
| hsa-miR-3940-3p | 3351 | 4372 | discovered in breast tumor | | |
| hsa-miR-3940-5p | 3352 | 4373 | discovered in breast tumor | | |
| hsa-miR-3941 | 3353 | 4374 | | | |
| hsa-miR-3942-3p | 3354 | 4375 | discovered in breast tumor and lymphoblastic leukaemia | | |
| hsa-miR-3942-5p | 3355 | 4376 | discovered in breast tumor and lymphoblastic leukaemia | | |
| hsa-miR-3943 | 3356 | 4377 | | | |
| hsa-miR-3944-3p | 3357 | 4378 | discovered in breast tumor | | |
| hsa-miR-3944-5p | 3358 | 4379 | discovered in breast tumor | | |
| hsa-miR-3945 | 3359 | 4380 | | | |
| hsa-miR-3960 | 3360 | 4381 | osteoblast | | |

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|---|---|---|---|---|---|
| hsa-miR-3972 | 3361 | 4382 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3973 | 3362 | 4383 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3974 | 3363 | 4384 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3975 | 3364 | 4385 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3976 | 3365 | 4386 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3977 | 3366 | 4387 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-3978 | 3367 | 4388 | discovered in Acute Myeloid Leukaemia | | |
| hsa-miR-409-3p | 3368 | 4389 | | gastric cancer | |
| hsa-miR-409-5p | 3369 | 4390 | | gastric cancer | |
| hsa-miR-410 | 3370 | 4391 | brain | glioma | |
| hsa-miR-411-3p | 3371 | 4392 | | Glioblastoma others | |
| hsa-miR-411-5p | 3372 | 4393 | | Glioblastoma others | |
| hsa-miR-412 | 3373 | 4394 | | upregulated in lung cancer | |
| hsa-miR-421 | 3374 | 4395 | endothelial cells | gastric cancer, HCC | |
| hsa-miR-422a | 3375 | 4396 | circulating microRNA (in plasma) | | |
| hsa-miR-423-3p | 3376 | 4397 | embryonic stem cells | | |
| hsa-miR-423-5p | 3377 | 4398 | heart, embryonic stem cells | | |
| hsa-miR-424-3p | 3378 | 4399 | endothelial cells | various cancers(e.g B-lieage ALL), cardiac diseases | pro-angiogenic |
| hsa-miR-424-5p | 3379 | 4400 | endothelial cells | various cancers(e.g B-lieage ALL), cardiac diseases | pro-angiogenic |
| hsa-miR-4251 | 3380 | 4401 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4252 | 3381 | 4402 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4253 | 3382 | 4403 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-425-3p | 3383 | 4404 | brain | ovarian cancer, brain tumor | |
| hsa-miR-4254 | 3384 | 4405 | discovered in | | |

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| | | | embryonic stem cells and neural precusors | | |
| hsa-miR-4255 | 3385 | 4406 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-425-5p | 3386 | 4407 | brain | B-lieage ALL, brain tumor | |
| hsa-miR-4256 | 3387 | 4408 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4257 | 3388 | 4409 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4258 | 3389 | 4410 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4259 | 3390 | 4411 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4260 | 3391 | 4412 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4261 | 3392 | 4413 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4262 | 3393 | 4414 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4263 | 3394 | 4415 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4264 | 3395 | 4416 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4265 | 3396 | 4417 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4266 | 3397 | 4418 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4267 | 3398 | 4419 | discovered in embryonic stem | | |

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|---|---|---|---|---|---|
| | | | cells and neural precusors | | |
| hsa-miR-4268 | 3399 | 4420 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4269 | 3400 | 4421 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4270 | 3401 | 4422 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4271 | 3402 | 4423 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4272 | 3403 | 4424 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4273 | 3404 | 4425 | | | |
| hsa-miR-4274 | 3405 | 4426 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4275 | 3406 | 4427 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4276 | 3407 | 4428 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4277 | 3408 | 4429 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4278 | 3409 | 4430 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4279 | 3410 | 4431 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4280 | 3411 | 4432 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4281 | 3412 | 4433 | discovered in embryonic stem cells and neural precusors | | |

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|---|---|---|---|---|---|
| hsa-miR-4282 | 3413 | 4434 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4283 | 3414 | 4435 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4284 | 3415 | 4436 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4285 | 3416 | 4437 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4286 | 3417 | 4438 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4287 | 3418 | 4439 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4288 | 3419 | 4440 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4289 | 3420 | 4441 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-429 | 3421 | 4442 | Epithelial cells | various cancers (colorectal, endometrial, gastric, ovarian etc) | |
| hsa-miR-4290 | 3422 | 4443 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4291 | 3423 | 4444 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4292 | 3424 | 4445 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4293 | 3425 | 4446 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4294 | 3426 | 4447 | discovered in embryonic stem | | |

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|---|---|---|---|---|---|
| | | | cells and neural precusors | | |
| hsa-miR-4295 | 3427 | 4448 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4296 | 3428 | 4449 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4297 | 3429 | 4450 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4298 | 3430 | 4451 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4299 | 3431 | 4452 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4300 | 3432 | 4453 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4301 | 3433 | 4454 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4302 | 3434 | 4455 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4303 | 3435 | 4456 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4304 | 3436 | 4457 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4305 | 3437 | 4458 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4306 | 3438 | 4459 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4307 | 3439 | 4460 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4308 | 3440 | 4461 | discovered in | | |

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|---|---|---|---|---|---|
| | | | embryonic stem cells and neural precusors | | |
| hsa-miR-4309 | 3441 | 4462 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4310 | 3442 | 4463 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4311 | 3443 | 4464 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4312 | 3444 | 4465 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4313 | 3445 | 4466 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-431-3p | 3446 | 4467 | | Cancers (follicular lymphoma) | |
| hsa-miR-4314 | 3447 | 4468 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4315 | 3448 | 4469 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-431-5p | 3449 | 4470 | | Cancers (follicular lymphoma) | |
| hsa-miR-4316 | 3450 | 4471 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4317 | 3451 | 4472 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4318 | 3452 | 4473 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4319 | 3453 | 4474 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4320 | 3454 | 4475 | discovered in embryonic stem | | |

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| | | | cells and neural precusors | | |
| hsa-miR-4321 | 3455 | 4476 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4322 | 3456 | 4477 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4323 | 3457 | 4478 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-432-3p | 3458 | 4479 | myoblast | | myogenic differentiation |
| hsa-miR-4324 | 3459 | 4480 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4325 | 3460 | 4481 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-432-5p | 3461 | 4482 | myoblast | | myogenic differentiation |
| hsa-miR-4326 | 3462 | 4483 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4327 | 3463 | 4484 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4328 | 3464 | 4485 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4329 | 3465 | 4486 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-433 | 3466 | 4487 | | various diseases (cancer, Parkinson's, Chondrodysplasia) | |
| hsa-miR-4330 | 3467 | 4488 | discovered in embryonic stem cells and neural precusors | | |
| hsa-miR-4417 | 3468 | 4489 | discovered in B cells | | |
| hsa-miR-4418 | 3469 | 4490 | discovered in B cells | | |

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|---|---|---|---|---|---|
| hsa-miR-4419a | 3470 | 4491 | discovered in B cells | | |
| hsa-miR-4419b | 3471 | 4492 | discovered in B cells | | |
| hsa-miR-4420 | 3472 | 4493 | discovered in B cells | | |
| hsa-miR-4421 | 3473 | 4494 | discovered in B cells | | |
| hsa-miR-4422 | 3474 | 4495 | discovered in breast tumor and B cells | | |
| hsa-miR-4423-3p | 3475 | 4496 | discovered in breast tumor, B cells and skin(psoriasis) | | |
| hsa-miR-4423-5p | 3476 | 4497 | discovered in breast tumor B cells and skin(psoriasis) | | |
| hsa-miR-4424 | 3477 | 4498 | discovered in B cells | | |
| hsa-miR-4425 | 3478 | 4499 | discovered in B cells | | |
| hsa-miR-4426 | 3479 | 4500 | discovered in B cells | | |
| hsa-miR-4427 | 3480 | 4501 | discovered in B cells | | |
| hsa-miR-4428 | 3481 | 4502 | discovered in B cells | | |
| hsa-miR-4429 | 3482 | 4503 | discovered in B cells | | |
| hsa-miR-4430 | 3483 | 4504 | discovered in B cells | | |
| hsa-miR-4431 | 3484 | 4505 | discovered in B cells | | |
| hsa-miR-4432 | 3485 | 4506 | discovered in B cells | | |
| hsa-miR-4433-3p | 3486 | 4507 | discovered in B cells | | |
| hsa-miR-4433-5p | 3487 | 4508 | discovered in B cells | | |
| hsa-miR-4434 | 3488 | 4509 | discovered in B cells | | |
| hsa-miR-4435 | 3489 | 4510 | discovered in B cells | | |
| hsa-miR-4436a | 3490 | 4511 | discovered in breast tumor and B cells | | |
| hsa-miR-4436b-3p | 3491 | 4512 | discovered in breast tumor | | |
| hsa-miR-4436b-5p | 3492 | 4513 | discovered in breast tumor | | |
| hsa-miR-4437 | 3493 | 4514 | discovered in B cells | | |
| hsa-miR-4438 | 3494 | 4515 | discovered in B cells | | |
| hsa-miR-4439 | 3495 | 4516 | discovered in B cells | | |
| hsa-miR-4440 | 3496 | 4517 | discovered in B | | |

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|---|---|---|---|---|---|
| | | | cells | | |
| hsa-miR-4441 | 3497 | 4518 | discovered in B cells | | |
| hsa-miR-4442 | 3498 | 4519 | discovered in B cells | | |
| hsa-miR-4443 | 3499 | 4520 | discovered in B cells | | |
| hsa-miR-4444 | 3500 | 4521 | discovered in B cells | | |
| hsa-miR-4445-3p | 3501 | 4522 | discovered in B cells | | |
| hsa-miR-4445-5p | 3502 | 4523 | discovered in B cells | | |
| hsa-miR-4446-3p | 3503 | 4524 | discovered in breast tumor and B cells | | |
| hsa-miR-4446-5p | 3504 | 4525 | discovered in breast tumor and B cells | | |
| hsa-miR-4447 | 3505 | 4526 | discovered in B cells | | |
| hsa-miR-4448 | 3506 | 4527 | discovered in B cells | | |
| hsa-miR-4449 | 3507 | 4528 | discovered in B cells | | |
| hsa-miR-4450 | 3508 | 4529 | discovered in B cells | | |
| hsa-miR-4451 | 3509 | 4530 | discovered in B cells | | |
| hsa-miR-4452 | 3510 | 4531 | discovered in B cells | | |
| hsa-miR-4453 | 3511 | 4532 | discovered in B cells | | |
| hsa-miR-4454 | 3512 | 4533 | discovered in B cells | | |
| hsa-miR-4455 | 3513 | 4534 | discovered in B cells | | |
| hsa-miR-4456 | 3514 | 4535 | discovered in B cells | | |
| hsa-miR-4457 | 3515 | 4536 | discovered in B cells | | |
| hsa-miR-4458 | 3516 | 4537 | discovered in B cells | | |
| hsa-miR-4459 | 3517 | 4538 | discovered in B cells | | |
| hsa-miR-4460 | 3518 | 4539 | discovered in B cells | | |
| hsa-miR-4461 | 3519 | 4540 | discovered in B cells | | |
| hsa-miR-4462 | 3520 | 4541 | discovered in B cells | | |
| hsa-miR-4463 | 3521 | 4542 | discovered in B cells | | |
| hsa-miR-4464 | 3522 | 4543 | discovered in B cells | | |
| hsa-miR-4465 | 3523 | 4544 | discovered in B cells | | |

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|---|---|---|---|---|---|
| hsa-miR-4466 | 3524 | 4545 | discovered in B cells | | |
| hsa-miR-4467 | 3525 | 4546 | discovered in breast tumor and B cells | | |
| hsa-miR-4468 | 3526 | 4547 | discovered in B cells | | |
| hsa-miR-4469 | 3527 | 4548 | discovered in breast tumor and B cells | | |
| hsa-miR-4470 | 3528 | 4549 | discovered in B cells | | |
| hsa-miR-4471 | 4550 | 5571 | discovered in breast tumor and B cells | | |
| hsa-miR-4472 | 4551 | 5572 | discovered in B cells | | |
| hsa-miR-4473 | 4552 | 5573 | discovered in B cells | | |
| hsa-miR-4474-3p | 4553 | 5574 | discovered in breast tumor, lymphoblastic leukaemia and B cells | | |
| hsa-miR-4474-5p | 4554 | 5575 | discovered in breast tumor, lymphoblastic leukaemia and B cells | | |
| hsa-miR-4475 | 4555 | 5576 | discovered in B cells | | |
| hsa-miR-4476 | 4556 | 5577 | discovered in B cells | | |
| hsa-miR-4477a | 4557 | 5578 | discovered in B cells | | |
| hsa-miR-4477b | 4558 | 5579 | discovered in B cells | | |
| hsa-miR-4478 | 4559 | 5580 | discovered in B cells | | |
| hsa-miR-4479 | 4560 | 5581 | discovered in B cells | | |
| hsa-miR-448 | 4561 | 5582 | liver(hepatocytes) | HCC | |
| hsa-miR-4480 | 4562 | 5583 | discovered in B cells | | |
| hsa-miR-4481 | 4563 | 5584 | discovered in B cells | | |
| hsa-miR-4482-3p | 4564 | 5585 | discovered in B cells | | |
| hsa-miR-4482-5p | 4565 | 5586 | discovered in B cells | | |
| hsa-miR-4483 | 4566 | 5587 | discovered in B cells | | |
| hsa-miR-4484 | 4567 | 5588 | discovered in B cells | | |
| hsa-miR-4485 | 4568 | 5589 | discovered in B cells | | |
| hsa-miR-4486 | 4569 | 5590 | discovered in B cells | | |

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|---|---|---|---|---|---|
| hsa-miR-4487 | 4570 | 5591 | discovered in B cells | | |
| hsa-miR-4488 | 4571 | 5592 | discovered in B cells | | |
| hsa-miR-4489 | 4572 | 5593 | discovered in breast tumor and B cells | | |
| hsa-miR-4490 | 4573 | 5594 | discovered in B cells | | |
| hsa-miR-4491 | 4574 | 5595 | discovered in B cells | | |
| hsa-miR-4492 | 4575 | 5596 | discovered in B cells | | |
| hsa-miR-4493 | 4576 | 5597 | discovered in B cells | | |
| hsa-miR-4494 | 4577 | 5598 | discovered in B cells | | |
| hsa-miR-4495 | 4578 | 5599 | discovered in B cells | | |
| hsa-miR-4496 | 4579 | 5600 | discovered in B cells | | |
| hsa-miR-4497 | 4580 | 5601 | discovered in B cells | | |
| hsa-miR-4498 | 4581 | 5602 | discovered in B cells | | |
| hsa-miR-4499 | 4582 | 5603 | discovered in B cells | | |
| hsa-miR-449a | 4583 | 5604 | chondrocytes,ciliated epithelial cells | lung, colonic, ovarian cancer | cell cycle progression and proliferation |
| hsa-miR-449b-3p | 4584 | 5605 | ciliated epithelial cells, other tissues | various cancer cells | cell cycle progression and proliferation |
| hsa-miR-449b-5p | 4585 | 5606 | ciliated epithelial cells, other tissues | various cancer cells | cell cycle progression and proliferation |
| hsa-miR-449c-3p | 4586 | 5607 | | epithelial ovarian cancer cells | |
| hsa-miR-449c-5p | 4587 | 5608 | | epithelial ovarian cancer cells | |
| hsa-miR-4500 | 4588 | 5609 | discovered in B cells | | |
| hsa-miR-4501 | 4589 | 5610 | discovered in B cells | | |
| hsa-miR-4502 | 4590 | 5611 | discovered in B cells | | |
| hsa-miR-4503 | 4591 | 5612 | discovered in B cells | | |
| hsa-miR-4504 | 4592 | 5613 | discovered in B cells | | |
| hsa-miR-4505 | 4593 | 5614 | discovered in B cells | | |
| hsa-miR-4506 | 4594 | 5615 | discovered in B cells | | |
| hsa-miR-4507 | 4595 | 5616 | discovered in B cells | | |

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|---|---|---|---|---|---|
| hsa-miR-4508 | 4596 | 5617 | discovered in B cells | | |
| hsa-miR-4509 | 4597 | 5618 | discovered in B cells | | |
| hsa-miR-450a-3p | 4598 | 5619 | | | |
| hsa-miR-450a-5p | 4599 | 5620 | | | |
| hsa-miR-450b-3p | 4600 | 5621 | | | |
| hsa-miR-450b-5p | 4601 | 5622 | | | |
| hsa-miR-4510 | 4602 | 5623 | discovered in B cells | | |
| hsa-miR-4511 | 4603 | 5624 | discovered in B cells | | |
| hsa-miR-4512 | 4604 | 5625 | discovered in B cells | | |
| hsa-miR-4513 | 4605 | 5626 | discovered in B cells | | |
| hsa-miR-4514 | 4606 | 5627 | discovered in B cells | | |
| hsa-miR-4515 | 4607 | 5628 | discovered in B cells | | |
| hsa-miR-4516 | 4608 | 5629 | discovered in B cells | | |
| hsa-miR-4517 | 4609 | 5630 | discovered in B cells | | |
| hsa-miR-4518 | 4610 | 5631 | discovered in B cells | | |
| hsa-miR-4519 | 4611 | 5632 | discovered in B cells | | |
| hsa-miR-451a | 4612 | 5633 | heart, central nevous system, epithelial cells | | |
| hsa-miR-451b | 4613 | 5634 | heart, central nevous system, epithelial cells | | |
| hsa-miR-4520a-3p | 4614 | 5635 | discovered in breast tumor and B cells, skin(psoriasis) | | |
| hsa-miR-4520a-5p | 4615 | 5636 | discovered in breast tumor and B cells, skin(psoriasis) | | |
| hsa-miR-4520b-3p | 4616 | 5637 | discovered in breast tumor | | |
| hsa-miR-4520b-5p | 4617 | 5638 | discovered in breast tumor | | |
| hsa-miR-4521 | 4618 | 5639 | discovered in B cells | | |
| hsa-miR-4522 | 4619 | 5640 | discovered in B cells | | |
| hsa-miR-4523 | 4620 | 5641 | discovered in B cells | | |
| hsa-miR-452-3p | 4621 | 5642 | myoblast | bladder cancer and others | |
| hsa-miR-4524a-3p | 4622 | 5643 | discovered in breast tumor and B cells, skin(psoriasis) | | |

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|---|---|---|---|---|---|
| hsa-miR-4524a-5p | 4623 | 5644 | discovered in breast tumor and B cells, skin(psoriasis) | | |
| hsa-miR-4524b-3p | 4624 | 5645 | discovered in breast tumor and B cells, skin(psoriasis) | | |
| hsa-miR-4524b-5p | 4625 | 5646 | discovered in breast tumor and B cells, skin(psoriasis) | | |
| hsa-miR-4525 | 4626 | 5647 | discovered in B cells | | |
| hsa-miR-452-5p | 4627 | 5648 | myoblast | bladder cancer and others | |
| hsa-miR-4526 | 4628 | 5649 | discovered in breast tumor and B cells | | |
| hsa-miR-4527 | 4629 | 5650 | discovered in B cells | | |
| hsa-miR-4528 | 4630 | 5651 | discovered in B cells | | |
| hsa-miR-4529-3p | 4631 | 5652 | discovered in breast tumor and B cells | | |
| hsa-miR-4529-5p | 4632 | 5653 | discovered in breast tumor and B cells | | |
| hsa-miR-4530 | 4633 | 5654 | discovered in B cells | | |
| hsa-miR-4531 | 4634 | 5655 | discovered in B cells | | |
| hsa-miR-4532 | 4635 | 5656 | discovered in B cells | | |
| hsa-miR-4533 | 4636 | 5657 | discovered in B cells | | |
| hsa-miR-4534 | 4637 | 5658 | discovered in B cells | | |
| hsa-miR-4535 | 4638 | 5659 | discovered in B cells | | |
| hsa-miR-4536-3p | 4639 | 5660 | discovered in B cells | | |
| hsa-miR-4536-5p | 4640 | 5661 | discovered in B cells | | |
| hsa-miR-4537 | 4641 | 5662 | discovered in B cells | | |
| hsa-miR-4538 | 4642 | 5663 | discovered in B cells | | |
| hsa-miR-4539 | 4643 | 5664 | discovered in B cells | | |
| hsa-miR-4540 | 4644 | 5665 | discovered in B cells | | |
| hsa-miR-454-3p | 4645 | 5666 | embryoid body cells, central nevous system, monocytes | | |
| hsa-miR-454-5p | 4646 | 5667 | embryoid body cells, central nevous system, monocytes | | |

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|---|---|---|---|---|---|
| hsa-miR-455-3p | 4647 | 5668 | | basal cell carcinoma, other cancers | |
| hsa-miR-455-5p | 4648 | 5669 | | basal cell carcinoma, other cancers | |
| hsa-miR-4632-3p | 4649 | 5670 | discovred in breast tumor | | |
| hsa-miR-4632-5p | 4650 | 5671 | discovered in breast tumor | | |
| hsa-miR-4633-3p | 4651 | 5672 | discovered in breast tumor | | |
| hsa-miR-4633-5p | 4652 | 5673 | discovered in breast tumor | | |
| hsa-miR-4634 | 4653 | 5674 | discovered in breast tumor | | |
| hsa-miR-4635 | 4654 | 5675 | discovered in breast tumor | | |
| hsa-miR-4636 | 4655 | 5676 | discovered in breast tumor | | |
| hsa-miR-4637 | 4656 | 5677 | discovered in breast tumor and lymphoblastic leukaemia | | |
| hsa-miR-4638-3p | 4657 | 5678 | discovered in breast tumor | | |
| hsa-miR-4638-5p | 4658 | 5679 | discovered in breast tumor | | |
| hsa-miR-4639-3p | 4659 | 5680 | discovered in breast tumor | | |
| hsa-miR-4639-5p | 4660 | 5681 | discovered in breast tumor | | |
| hsa-miR-4640-3p | 4661 | 5682 | discovered in breast tumor | | |
| hsa-miR-4640-5p | 4662 | 5683 | discovered in breast tumor | | |
| hsa-miR-4641 | 4663 | 5684 | discovered in breast tumor | | |
| hsa-miR-4642 | 4664 | 5685 | discovered in breast tumor | | |
| hsa-miR-4643 | 4665 | 5686 | discovered in breast tumor | | |
| hsa-miR-4644 | 4666 | 5687 | discovered in breast tumor | | |
| hsa-miR-4645-3p | 4667 | 5688 | discovered in breast tumor | | |
| hsa-miR-4645-5p | 4668 | 5689 | discovered in breast tumor | | |
| hsa-miR-4646-3p | 4669 | 5690 | discovered in breast tumor | | |
| hsa-miR-4646-5p | 4670 | 5691 | discovered in breast tumor | | |
| hsa-miR-4647 | 4671 | 5692 | discovered in breast tumor | | |
| hsa-miR-4648 | 4672 | 5693 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4649-3p | 4673 | 5694 | discovered in breast tumor | | |
| hsa-miR-4649-5p | 4674 | 5695 | discovered in breast tumor | | |
| hsa-miR-4650-3p | 4675 | 5696 | discovered in breast tumor | | |
| hsa-miR-4650-5p | 4676 | 5697 | discovered in breast tumor | | |
| hsa-miR-4651 | 4677 | 5698 | discovered in breast tumor | | |
| hsa-miR-4652-3p | 4678 | 5699 | discovered in breast tumor | | |
| hsa-miR-4652-5p | 4679 | 5700 | discovered in breast tumor | | |
| hsa-miR-4653-3p | 4680 | 5701 | discovered in breast tumor | | |
| hsa-miR-4653-5p | 4681 | 5702 | discovered in breast tumor | | |
| hsa-miR-4654 | 4682 | 5703 | discovered in breast tumor | | |
| hsa-miR-4655-3p | 4683 | 5704 | discovered in breast tumor | | |
| hsa-miR-4655-5p | 4684 | 5705 | discovered in breast tumor | | |
| hsa-miR-4656 | 4685 | 5706 | discovered in breast tumor | | |
| hsa-miR-4657 | 4686 | 5707 | discovered in breast tumor | | |
| hsa-miR-4658 | 4687 | 5708 | discovered in breast tumor | | |
| hsa-miR-4659a-3p | 4688 | 5709 | discovered in breast tumor | | |
| hsa-miR-4659a-5p | 4689 | 5710 | discovered in breast tumor | | |
| hsa-miR-4659b-3p | 4690 | 5711 | discovered in breast tumor | | |
| hsa-miR-4659b-5p | 4691 | 5712 | discovered in breast tumor | | |
| hsa-miR-466 | 4692 | 5713 | | | |
| hsa-miR-4660 | 4693 | 5714 | discovered in breast tumor | | |
| hsa-miR-4661-3p | 4694 | 5715 | discovered in breast tumor | | |
| hsa-miR-4661-5p | 4695 | 5716 | discovered in breast tumor | | |
| hsa-miR-4662a-3p | 4696 | 5717 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4662a-5p | 4697 | 5718 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4662b | 4698 | 5719 | discovered in breast tumor | | |
| hsa-miR-4663 | 4699 | 5720 | discovered in breast tumor | | |
| hsa-miR-4664-3p | 4700 | 5721 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4664-5p | 4701 | 5722 | discovered in breast tumor | | |
| hsa-miR-4665-3p | 4702 | 5723 | discovered in breast tumor | | |
| hsa-miR-4665-5p | 4703 | 5724 | discovered in breast tumor | | |
| hsa-miR-4666a-3p | 4704 | 5725 | discovered in breast tumor | | |
| hsa-miR-4666a-5p | 4705 | 5726 | discovered in breast tumor | | |
| hsa-miR-4666b | 4706 | 5727 | | | |
| hsa-miR-4667-3p | 4707 | 5728 | discovered in breast tumor | | |
| hsa-miR-4667-5p | 4708 | 5729 | discovered in breast tumor | | |
| hsa-miR-4668-3p | 4709 | 5730 | discovered in breast tumor | | |
| hsa-miR-4668-5p | 4710 | 5731 | discovered in breast tumor | | |
| hsa-miR-4669 | 4711 | 5732 | discovered in breast tumor | | |
| hsa-miR-4670-3p | 4712 | 5733 | discovered in breast tumor | | |
| hsa-miR-4670-5p | 4713 | 5734 | discovered in breast tumor | | |
| hsa-miR-4671-3p | 4714 | 5735 | discovered in breast tumor | | |
| hsa-miR-4671-5p | 4715 | 5736 | discovered in breast tumor | | |
| hsa-miR-4672 | 4716 | 5737 | discovered in breast tumor | | |
| hsa-miR-4673 | 4717 | 5738 | discovered in breast tumor | | |
| hsa-miR-4674 | 4718 | 5739 | discovered in breast tumor | | |
| hsa-miR-4675 | 4719 | 5740 | discovered in breast tumor | | |
| hsa-miR-4676-3p | 4720 | 5741 | discovered in breast tumor | | |
| hsa-miR-4676-5p | 4721 | 5742 | discovered in breast tumor | | |
| hsa-miR-4677-3p | 4722 | 5743 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4677-5p | 4723 | 5744 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4678 | 4724 | 5745 | discovered in breast tumor | | |
| hsa-miR-4679 | 4725 | 5746 | discovered in breast tumor | | |
| hsa-miR-4680-3p | 4726 | 5747 | discovered in breast tumor | | |
| hsa-miR-4680-5p | 4727 | 5748 | discovered in breast tumor | | |
| hsa-miR-4681 | 4728 | 5749 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4682 | 4729 | 5750 | discovered in breast tumor | | |
| hsa-miR-4683 | 4730 | 5751 | discovered in breast tumor | | |
| hsa-miR-4684-3p | 4731 | 5752 | discovered in breast tumor | | |
| hsa-miR-4684-5p | 4732 | 5753 | discovered in breast tumor | | |
| hsa-miR-4685-3p | 4733 | 5754 | discovered in breast tumor | | |
| hsa-miR-4685-5p | 4734 | 5755 | discovered in breast tumor | | |
| hsa-miR-4686 | 4735 | 5756 | discovered in breast tumor | | |
| hsa-miR-4687-3p | 4736 | 5757 | discovered in breast tumor | | |
| hsa-miR-4687-5p | 4737 | 5758 | discovered in breast tumor | | |
| hsa-miR-4688 | 4738 | 5759 | discovered in breast tumor | | |
| hsa-miR-4689 | 4739 | 5760 | discovered in breast tumor | | |
| hsa-miR-4690-3p | 4740 | 5761 | discovered in breast tumor | | |
| hsa-miR-4690-5p | 4741 | 5762 | discovered in breast tumor | | |
| hsa-miR-4691-3p | 4742 | 5763 | discovered in breast tumor | | |
| hsa-miR-4691-5p | 4743 | 5764 | discovered in breast tumor | | |
| hsa-miR-4692 | 4744 | 5765 | discovered in breast tumor | | |
| hsa-miR-4693-3p | 4745 | 5766 | discovered in breast tumor | | |
| hsa-miR-4693-5p | 4746 | 5767 | discovered in breast tumor | | |
| hsa-miR-4694-3p | 4747 | 5768 | discovered in breast tumor | | |
| hsa-miR-4694-5p | 4748 | 5769 | discovered in breast tumor | | |
| hsa-miR-4695-3p | 4749 | 5770 | discovered in breast tumor | | |
| hsa-miR-4695-5p | 4750 | 5771 | discovered in breast tumor | | |
| hsa-miR-4696 | 4751 | 5772 | discovered in breast tumor | | |
| hsa-miR-4697-3p | 4752 | 5773 | discovered in breast tumor | | |
| hsa-miR-4697-5p | 4753 | 5774 | discovered in breast tumor | | |
| hsa-miR-4698 | 4754 | 5775 | discovered in breast tumor | | |
| hsa-miR-4699-3p | 4755 | 5776 | discovered in breast tumor | | |

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|---|---|---|---|---|---|
| hsa-miR-4699-5p | 4756 | 5777 | discovered in breast tumor | | |
| hsa-miR-4700-3p | 4757 | 5778 | discovered in breast tumor | | |
| hsa-miR-4700-5p | 4758 | 5779 | discovered in breast tumor | | |
| hsa-miR-4701-3p | 4759 | 5780 | discovered in breast tumor | | |
| hsa-miR-4701-5p | 4760 | 5781 | discovered in breast tumor | | |
| hsa-miR-4703-3p | 4761 | 5782 | discovered in breast tumor | | |
| hsa-miR-4703-5p | 4762 | 5783 | discovered in breast tumor | | |
| hsa-miR-4704-3p | 4763 | 5784 | discovered in breast tumor | | |
| hsa-miR-4704-5p | 4764 | 5785 | discovered in breast tumor | | |
| hsa-miR-4705 | 4765 | 5786 | discovered in breast tumor | | |
| hsa-miR-4706 | 4766 | 5787 | discovered in breast tumor | | |
| hsa-miR-4707-3p | 4767 | 5788 | discovered in breast tumor | | |
| hsa-miR-4707-5p | 4768 | 5789 | discovered in breast tumor | | |
| hsa-miR-4708-3p | 4769 | 5790 | discovered in breast tumor | | |
| hsa-miR-4708-5p | 4770 | 5791 | discovered in breast tumor | | |
| hsa-miR-4709-3p | 4771 | 5792 | discovered in breast tumor | | |
| hsa-miR-4709-5p | 4772 | 5793 | discovered in breast tumor | | |
| hsa-miR-4710 | 4773 | 5794 | discovered in breast tumor | | |
| hsa-miR-4711-3p | 4774 | 5795 | discovered in breast tumor | | |
| hsa-miR-4711-5p | 4775 | 5796 | discovered in breast tumor | | |
| hsa-miR-4712-3p | 4776 | 5797 | discovered in breast tumor | | |
| hsa-miR-4712-5p | 4777 | 5798 | discovered in breast tumor | | |
| hsa-miR-4713-3p | 4778 | 5799 | discovered in breast tumor | | |
| hsa-miR-4713-5p | 4779 | 5800 | discovered in breast tumor | | |
| hsa-miR-4714-3p | 4780 | 5801 | discovered in breast tumor | | |
| hsa-miR-4714-5p | 4781 | 5802 | discovered in breast tumor | | |
| hsa-miR-4715-3p | 4782 | 5803 | discovered in breast tumor | | |
| hsa-miR-4715-5p | 4783 | 5804 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4716-3p | 4784 | 5805 | discovered in breast tumor | | |
| hsa-miR-4716-5p | 4785 | 5806 | discovered in breast tumor | | |
| hsa-miR-4717-3p | 4786 | 5807 | discovered in breast tumor | | |
| hsa-miR-4717-5p | 4787 | 5808 | discovered in breast tumor | | |
| hsa-miR-4718 | 4788 | 5809 | discovered in breast tumor | | |
| hsa-miR-4719 | 4789 | 5810 | discovered in breast tumor | | |
| hsa-miR-4720-3p | 4790 | 5811 | discovered in breast tumor | | |
| hsa-miR-4720-5p | 4791 | 5812 | discovered in breast tumor | | |
| hsa-miR-4721 | 4792 | 5813 | discovered in breast tumor | | |
| hsa-miR-4722-3p | 4793 | 5814 | discovered in breast tumor | | |
| hsa-miR-4722-5p | 4794 | 5815 | discovered in breast tumor | | |
| hsa-miR-4723-3p | 4795 | 5816 | discovered in breast tumor | | |
| hsa-miR-4723-5p | 4796 | 5817 | discovered in breast tumor | | |
| hsa-miR-4724-3p | 4797 | 5818 | discovered in breast tumor | | |
| hsa-miR-4724-5p | 4798 | 5819 | discovered in breast tumor | | |
| hsa-miR-4725-3p | 4799 | 5820 | discovered in breast tumor | | |
| hsa-miR-4725-5p | 4800 | 5821 | discovered in breast tumor | | |
| hsa-miR-4726-3p | 4801 | 5822 | discovered in breast tumor | | |
| hsa-miR-4726-5p | 4802 | 5823 | discovered in breast tumor | | |
| hsa-miR-4727-3p | 4803 | 5824 | discovered in breast tumor | | |
| hsa-miR-4727-5p | 4804 | 5825 | discovered in breast tumor | | |
| hsa-miR-4728-3p | 4805 | 5826 | discovered in breast tumor | | |
| hsa-miR-4728-5p | 4806 | 5827 | discovered in breast tumor | | |
| hsa-miR-4729 | 4807 | 5828 | discovered in breast tumor | | |
| hsa-miR-4730 | 4808 | 5829 | discovered in breast tumor | | |
| hsa-miR-4731-3p | 4809 | 5830 | discovered in breast tumor | | |
| hsa-miR-4731-5p | 4810 | 5831 | discovered in breast tumor | | |

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|---|---|---|---|---|---|
| hsa-miR-4732-3p | 4811 | 5832 | discovered in breast tumor | | |
| hsa-miR-4732-5p | 4812 | 5833 | discovered in breast tumor | | |
| hsa-miR-4733-3p | 4813 | 5834 | discovered in breast tumor | | |
| hsa-miR-4733-5p | 4814 | 5835 | discovered in breast tumor | | |
| hsa-miR-4734 | 4815 | 5836 | discovered in breast tumor | | |
| hsa-miR-4735-3p | 4816 | 5837 | discovered in breast tumor | | |
| hsa-miR-4735-5p | 4817 | 5838 | discovered in breast tumor | | |
| hsa-miR-4736 | 4818 | 5839 | discovered in breast tumor | | |
| hsa-miR-4737 | 4819 | 5840 | discovered in breast tumor | | |
| hsa-miR-4738-3p | 4820 | 5841 | discovered in breast tumor | | |
| hsa-miR-4738-5p | 4821 | 5842 | discovered in breast tumor | | |
| hsa-miR-4739 | 4822 | 5843 | discovered in breast tumor | | |
| hsa-miR-4740-3p | 4823 | 5844 | discovered in breast tumor | | |
| hsa-miR-4740-5p | 4824 | 5845 | discovered in breast tumor | | |
| hsa-miR-4741 | 4825 | 5846 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4742-3p | 4826 | 5847 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4742-5p | 4827 | 5848 | discovered in breast tumor | | |
| hsa-miR-4743-3p | 4828 | 5849 | discovered in breast tumor | | |
| hsa-miR-4743-5p | 4829 | 5850 | discovered in breast tumor | | |
| hsa-miR-4744 | 4830 | 5851 | discovered in breast tumor | | |
| hsa-miR-4745-3p | 4831 | 5852 | discovered in breast tumor | | |
| hsa-miR-4745-5p | 4832 | 5853 | discovered in breast tumor | | |
| hsa-miR-4746-3p | 4833 | 5854 | discovered in breast tumor | | |
| hsa-miR-4746-5p | 4834 | 5855 | discovered in breast tumor | | |
| hsa-miR-4747-3p | 4835 | 5856 | discovered in breast tumor | | |
| hsa-miR-4747-5p | 4836 | 5857 | discovered in breast tumor | | |
| hsa-miR-4748 | 4837 | 5858 | discovered in breast tumor | | |
| hsa-miR-4749-3p | 4838 | 5859 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4749-5p | 4839 | 5860 | discovered in breast tumor | | |
| hsa-miR-4750-3p | 4840 | 5861 | discovered in breast tumor | | |
| hsa-miR-4750-5p | 4841 | 5862 | discovered in breast tumor | | |
| hsa-miR-4751 | 4842 | 5863 | discovered in breast tumor | | |
| hsa-miR-4752 | 4843 | 5864 | discovered in breast tumor | | |
| hsa-miR-4753-3p | 4844 | 5865 | discovered in breast tumor | | |
| hsa-miR-4753-5p | 4845 | 5866 | discovered in breast tumor | | |
| hsa-miR-4754 | 4846 | 5867 | discovered in breast tumor | | |
| hsa-miR-4755-3p | 4847 | 5868 | discovered in breast tumor | | |
| hsa-miR-4755-5p | 4848 | 5869 | discovered in breast tumor | | |
| hsa-miR-4756-3p | 4849 | 5870 | discovered in breast tumor | | |
| hsa-miR-4756-5p | 4850 | 5871 | discovered in breast tumor | | |
| hsa-miR-4757-3p | 4851 | 5872 | discovered in breast tumor | | |
| hsa-miR-4757-5p | 4852 | 5873 | discovered in breast tumor | | |
| hsa-miR-4758-3p | 4853 | 5874 | discovered in breast tumor | | |
| hsa-miR-4758-5p | 4854 | 5875 | discovered in breast tumor | | |
| hsa-miR-4759 | 4855 | 5876 | discovered in breast tumor | | |
| hsa-miR-4760-3p | 4856 | 5877 | discovered in breast tumor | | |
| hsa-miR-4760-5p | 4857 | 5878 | discovered in breast tumor | | |
| hsa-miR-4761-3p | 4858 | 5879 | discovered in breast tumor | | |
| hsa-miR-4761-5p | 4859 | 5880 | discovered in breast tumor | | |
| hsa-miR-4762-3p | 4860 | 5881 | discovered in breast tumor | | |
| hsa-miR-4762-5p | 4861 | 5882 | discovered in breast tumor | | |
| hsa-miR-4763-3p | 4862 | 5883 | discovered in breast tumor | | |
| hsa-miR-4763-5p | 4863 | 5884 | discovered in breast tumor | | |
| hsa-miR-4764-3p | 4864 | 5885 | discovered in breast tumor | | |
| hsa-miR-4764-5p | 4865 | 5886 | discovered in breast tumor | | |

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|---|---|---|---|---|---|
| hsa-miR-4765 | 4866 | 5887 | discovered in breast tumor | | |
| hsa-miR-4766-3p | 4867 | 5888 | discovered in breast tumor | | |
| hsa-miR-4766-5p | 4868 | 5889 | discovered in breast tumor | | |
| hsa-miR-4767 | 4869 | 5890 | discovered in breast tumor | | |
| hsa-miR-4768-3p | 4870 | 5891 | discovered in breast tumor | | |
| hsa-miR-4768-5p | 4871 | 5892 | discovered in breast tumor | | |
| hsa-miR-4769-3p | 4872 | 5893 | discovered in breast tumor | | |
| hsa-miR-4769-5p | 4873 | 5894 | discovered in breast tumor | | |
| hsa-miR-4770 | 4874 | 5895 | discovered in breast tumor | | |
| hsa-miR-4771 | 4875 | 5896 | discovered in breast tumor | | |
| hsa-miR-4772-3p | 4876 | 5897 | discovered in breast tumor, blood monoclear cells | energy metabolism/ obesity | |
| hsa-miR-4772-5p | 4877 | 5898 | discovered in breast tumor, blood monoclear cells | energy metabolism/ obesity | |
| hsa-miR-4773 | 4878 | 5899 | discovered in breast tumor | | |
| hsa-miR-4774-3p | 4879 | 5900 | discovered in breast tumor and Lymphoblastic leukemia | | |
| hsa-miR-4774-5p | 4880 | 5901 | discovered in breast tumor and Lymphoblastic leukemia | | |
| hsa-miR-4775 | 4881 | 5902 | discovered in breast tumor | | |
| hsa-miR-4776-3p | 4882 | 5903 | discovered in breast tumor | | |
| hsa-miR-4776-5p | 4883 | 5904 | discovered in breast tumor | | |
| hsa-miR-4777-3p | 4884 | 5905 | discovered in breast tumor | | |
| hsa-miR-4777-5p | 4885 | 5906 | discovered in breast tumor | | |
| hsa-miR-4778-3p | 4886 | 5907 | discovered in breast tumor | | |
| hsa-miR-4778-5p | 4887 | 5908 | discovered in breast tumor | | |
| hsa-miR-4779 | 4888 | 5909 | discovered in breast tumor | | |
| hsa-miR-4780 | 4889 | 5910 | discovered in breast tumor | | |
| hsa-miR-4781-3p | 4890 | 5911 | discovered in breast | | |

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|---|---|---|---|---|---|
| | | | tumor | | |
| hsa-miR-4781-5p | 4891 | 5912 | discovered in breast tumor | | |
| hsa-miR-4782-3p | 4892 | 5913 | discovered in breast tumor | | |
| hsa-miR-4782-5p | 4893 | 5914 | discovered in breast tumor | | |
| hsa-miR-4783-3p | 4894 | 5915 | discovered in breast tumor | | |
| hsa-miR-4783-5p | 4895 | 5916 | discovered in breast tumor | | |
| hsa-miR-4784 | 4896 | 5917 | discovered in breast tumor | | |
| hsa-miR-4785 | 4897 | 5918 | discovered in breast tumor | | |
| hsa-miR-4786-3p | 4898 | 5919 | discovered in breast tumor | | |
| hsa-miR-4786-5p | 4899 | 5920 | discovered in breast tumor | | |
| hsa-miR-4787-3p | 4900 | 5921 | discovered in breast tumor | | |
| hsa-miR-4787-5p | 4901 | 5922 | discovered in breast tumor | | |
| hsa-miR-4788 | 4902 | 5923 | discovered in breast tumor | | |
| hsa-miR-4789-3p | 4903 | 5924 | discovered in breast tumor | | |
| hsa-miR-4789-5p | 4904 | 5925 | discovered in breast tumor | | |
| hsa-miR-4790-3p | 4905 | 5926 | discovered in breast tumor | | |
| hsa-miR-4790-5p | 4906 | 5927 | discovered in breast tumor | | |
| hsa-miR-4791 | 4907 | 5928 | discovered in breast tumor | | |
| hsa-miR-4792 | 4908 | 5929 | discovered in breast tumor | | |
| hsa-miR-4793-3p | 4909 | 5930 | discovered in breast tumor | | |
| hsa-miR-4793-5p | 4910 | 5931 | discovered in breast tumor | | |
| hsa-miR-4794 | 4911 | 5932 | discovered in breast tumor | | |
| hsa-miR-4795-3p | 4912 | 5933 | discovered in breast tumor | | |
| hsa-miR-4795-5p | 4913 | 5934 | discovered in breast tumor | | |
| hsa-miR-4796-3p | 4914 | 5935 | discovered in breast tumor | | |
| hsa-miR-4796-5p | 4915 | 5936 | discovered in breast tumor | | |
| hsa-miR-4797-3p | 4916 | 5937 | discovered in breast tumor | | |
| hsa-miR-4797-5p | 4917 | 5938 | discovered in breast tumor | | |

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|---|---|---|---|---|---|
| hsa-miR-4798-3p | 4918 | 5939 | discovered in breast tumor | | |
| hsa-miR-4798-5p | 4919 | 5940 | discovered in breast tumor | | |
| hsa-miR-4799-3p | 4920 | 5941 | discovered in breast tumor | | |
| hsa-miR-4799-5p | 4921 | 5942 | discovered in breast tumor | | |
| hsa-miR-4800-3p | 4922 | 5943 | discovered in breast tumor | | |
| hsa-miR-4800-5p | 4923 | 5944 | discovered in breast tumor | | |
| hsa-miR-4801 | 4924 | 5945 | discovered in breast tumor | | |
| hsa-miR-4802-3p | 4925 | 5946 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4802-5p | 4926 | 5947 | discovered in breast tumor, psoriasis | | |
| hsa-miR-4803 | 4927 | 5948 | discovered in breast tumor | | |
| hsa-miR-4804-3p | 4928 | 5949 | discovered in breast tumor | | |
| hsa-miR-4804-5p | 4929 | 5950 | discovered in breast tumor | | |
| hsa-miR-483-3p | 4930 | 5951 | | aderonocortical carcinoma, rectal/pancreatic cancer, proliferation of wounded epithelial cells | oncogenic |
| hsa-miR-483-5p | 4931 | 5952 | cartilage (chondrocyte), fetal brain | aderonocortical carcinoma | angiogenesis |
| hsa-miR-484 | 4932 | 5953 | | | mitochondrial network |
| hsa-miR-485-3p | 4933 | 5954 | | | |
| hsa-miR-485-5p | 4934 | 5955 | | ovarian epithelial tumor | |
| hsa-miR-486-3p | 4935 | 5956 | erythroid cells | various cancers | |
| hsa-miR-486-5p | 4936 | 5957 | stem cells (adipose) | various cancers | |
| hsa-miR-487a | 4937 | 5958 | | laryngeal carcinoma | |
| hsa-miR-487b | 4938 | 5959 | | neuroblastoma,pulmonary carcinogenesis | |
| hsa-miR-488-3p | 4939 | 5960 | | prostate cancer, others | |
| hsa-miR-488-5p | 4940 | 5961 | | prostate cancer, others | |
| hsa-miR-489 | 4941 | 5962 | mesenchymal stem cells | osteogenesis | |
| hsa-miR-490-3p | 4942 | 5963 | | neuroblastoma, terine leiomyoma (ULM)/muscle | |

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|---|---|---|---|---|---|
| hsa-miR-490-5p | 4943 | 5964 | | neuroblastoma, terine leiomyoma (ULM)/muscle | |
| hsa-miR-491-3p | 4944 | 5965 | | various cancers, brain disease | pro-apoptosis |
| hsa-miR-491-5p | 4945 | 5966 | | various cancers, brain disease | pro-apoptosis |
| hsa-miR-492 | 4946 | 5967 | | | |
| hsa-miR-493-3p | 4947 | 5968 | myeloid cells, pancreas (islet) | | |
| hsa-miR-493-5p | 4948 | 5969 | myeloid cells, pancreas (islet) | | |
| hsa-miR-494 | 4949 | 5970 | epithelial cells | various cancers | cell cycle |
| hsa-miR-495-3p | 4950 | 5971 | platelet | various cancers (gastric, MLL leukemia, pancreatic etc) and inflammation | |
| hsa-miR-495-5p | 4951 | 5972 | platelet | various cancers (gastric, MLL leukemia, pancreatic etc) and inflammation | |
| hsa-miR-496 | 4952 | 5973 | Blood | | |
| hsa-miR-497-3p | 4953 | 5974 | | various cancers (breast, colorectal, etc) | tumor supressor/pro-apoptosis |
| hsa-miR-497-5p | 4954 | 5975 | | various cancers (breast, colorectal, etc) | tumor supressor/pro-apoptosis |
| hsa-miR-498 | 4955 | 5976 | | autoimmuno (e.g. rheumatoid arthritis) | |
| hsa-miR-4999-3p | 4956 | 5977 | | | |
| hsa-miR-4999-5p | 4957 | 5978 | | | |
| hsa-miR-499a-3p | 4958 | 5979 | heart, cardiac stem cells | cardiovascular disease | cardiomyocyte differentiation |
| hsa-miR-499a-5p | 4959 | 5980 | heart, cardiac stem cells | cardiovascular disease | cardiomyocyte differentiation |
| hsa-miR-499b-3p | 4960 | 5981 | heart, cardiac stem cells | cardiovascular disease | cardiomyocyte differentiation |
| hsa-miR-499b-5p | 4961 | 5982 | heart, cardiac stem cells | cardiovascular disease | cardiomyocyte differentiation |
| hsa-miR-5000-3p | 4962 | 5983 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5000-5p | 4963 | 5984 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5001-3p | 4964 | 5985 | | | |
| hsa-miR-5001-5p | 4965 | 5986 | | | |
| hsa-miR-5002-3p | 4966 | 5987 | | | |
| hsa-miR-5002-5p | 4967 | 5988 | | | |
| hsa-miR-5003-3p | 4968 | 5989 | | | |
| hsa-miR-5003-5p | 4969 | 5990 | | | |

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|---|---|---|---|---|---|
| hsa-miR-5004-3p | 4970 | 5991 | | | |
| hsa-miR-5004-5p | 4971 | 5992 | | | |
| hsa-miR-5006-3p | 4972 | 5993 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5006-5p | 4973 | 5994 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5007-3p | 4974 | 5995 | | | |
| hsa-miR-5007-5p | 4975 | 5996 | | | |
| hsa-miR-5008-3p | 4976 | 5997 | | | |
| hsa-miR-5008-5p | 4977 | 5998 | | | |
| hsa-miR-5009-3p | 4978 | 5999 | | | |
| hsa-miR-5009-5p | 4979 | 6000 | | | |
| hsa-miR-500a-3p | 4980 | 6001 | | | |
| hsa-miR-500a-5p | 4981 | 6002 | | | |
| hsa-miR-500b | 4982 | 6003 | Blood (plasma) | | |
| hsa-miR-5010-3p | 4983 | 6004 | | abnormal skin (psoriasis) | |
| hsa-miR-5010-5p | 4984 | 6005 | | abnormal skin (psoriasis) | |
| hsa-miR-5011-3p | 4985 | 6006 | | | |
| hsa-miR-5011-5p | 4986 | 6007 | | | |
| hsa-miR-501-3p | 4987 | 6008 | | | |
| hsa-miR-501-5p | 4988 | 6009 | | | |
| hsa-miR-502-3p | 4989 | 6010 | | various cancers ( hepatocellular, ovarian, breast) | |
| hsa-miR-502-5p | 4990 | 6011 | | various cancers ( hepatocellular, ovarian, breast) | |
| hsa-miR-503-3p | 4991 | 6012 | ovary | | |
| hsa-miR-503-5p | 4992 | 6013 | ovary | | |
| hsa-miR-504 | 4993 | 6014 | | glioblastoma | |
| hsa-miR-5047 | 4994 | 6015 | | | |
| hsa-miR-505-3p | 4995 | 6016 | | breast cancer | |
| hsa-miR-505-5p | 4996 | 6017 | | breast cancer | |
| hsa-miR-506-3p | 4997 | 6018 | | various cancers | |
| hsa-miR-506-5p | 4998 | 6019 | | various cancers | |
| hsa-miR-507 | 4999 | 6020 | | | |
| hsa-miR-508-3p | 5000 | 6021 | | renal cell carcinoma | |
| hsa-miR-508-5p | 5001 | 6022 | endothelial progenitor cells (EPCs) | | |
| hsa-miR-5087 | 5002 | 6023 | | | |
| hsa-miR-5088 | 5003 | 6024 | | | |
| hsa-miR-5089-3p | 5004 | 6025 | | | |
| hsa-miR-5089-5p | 5005 | 6026 | | | |
| hsa-miR-5090 | 5006 | 6027 | | | |
| hsa-miR-5091 | 5007 | 6028 | | | |
| hsa-miR-5092 | 5008 | 6029 | | | |
| hsa-miR-5093 | 5009 | 6030 | | | |
| hsa-miR-509-3-5p | 5010 | 6031 | testis | | |

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| hsa-miR-509-3p | 5011 | 6032 | | renal cell carcinoma, brain disease | |
| hsa-miR-5094 | 5012 | 6033 | | | |
| hsa-miR-5095 | 5013 | 6034 | | cervical cancer | |
| hsa-miR-509-5p | 5014 | 6035 | | metabolic syndrome, brain disease | |
| hsa-miR-5096 | 5015 | 6036 | | cervical cance | |
| hsa-miR-510 | 5016 | 6037 | brain | | |
| hsa-miR-5100 | 5017 | 6038 | discoverd in Salivary gland | | |
| hsa-miR-511 | 5018 | 6039 | dendritic cells and macrophages | | |
| hsa-miR-512-3p | 5019 | 6040 | embryonic stem cells, placenta | | |
| hsa-miR-512-5p | 5020 | 6041 | embryonic stem cells, placenta, | | |
| hsa-miR-513a-3p | 5021 | 6042 | | lung carcinoma | |
| hsa-miR-513a-5p | 5022 | 6043 | endothelial cells | | |
| hsa-miR-513b | 5023 | 6044 | | follicular lymphoma | |
| hsa-miR-513c-3p | 5024 | 6045 | | | |
| hsa-miR-513c-5p | 5025 | 6046 | | | |
| hsa-miR-514a-3p | 5026 | 6047 | | | |
| hsa-miR-514a-5p | 5027 | 6048 | | | |
| hsa-miR-514b-3p | 5028 | 6049 | | various cancer cells | |
| hsa-miR-514b-5p | 5029 | 6050 | | various cancer cells | |
| hsa-miR-515-3p | 5030 | 6051 | | | |
| hsa-miR-515-5p | 5031 | 6052 | placenta | | |
| hsa-miR-516a-3p | 5032 | 6053 | frontal cortex | | |
| hsa-miR-516a-5p | 5033 | 6054 | placenta | | |
| hsa-miR-516b-3p | 5034 | 6055 | | | |
| hsa-miR-516b-5p | 5035 | 6056 | | | |
| hsa-miR-517-5p | 5036 | 6057 | placenta | | |
| hsa-miR-517a-3p | 5037 | 6058 | placenta | | |
| hsa-miR-517b-3p | 5038 | 6059 | placenta | | |
| hsa-miR-517c-3p | 5039 | 6060 | placenta | | |
| hsa-miR-5186 | 5040 | 6061 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5187-3p | 5041 | 6062 | discovered in lymphoblastic leukaemia, skin (psoriasis) | | |
| hsa-miR-5187-5p | 5042 | 6063 | discovered in lymphoblastic leukaemia, skin (psoriasis) | | |
| hsa-miR-5188 | 5043 | 6064 | discovered in lymphoblastic leukaemia | | |

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|---|---|---|---|---|---|
| hsa-miR-5189 | 5044 | 6065 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-518a-3p | 5045 | 6066 | | HCC | |
| hsa-miR-518a-5p | 5046 | 6067 | | various cancer cells | |
| hsa-miR-518b | 5047 | 6068 | placenta | HCC | cell cycle progression |
| hsa-miR-518c-3p | 5048 | 6069 | placenta | | |
| hsa-miR-518c-5p | 5049 | 6070 | placenta | | |
| hsa-miR-518d-3p | 5050 | 6071 | | | |
| hsa-miR-518d-5p | 5051 | 6072 | | | |
| hsa-miR-518e-3p | 5052 | 6073 | | HCC | cell cycle progression |
| hsa-miR-518e-5p | 5053 | 6074 | | HCC | cell cycle progression |
| hsa-miR-518f-3p | 5054 | 6075 | placenta | | |
| hsa-miR-518f-5p | 5055 | 6076 | placenta | | |
| hsa-miR-5190 | 5056 | 6077 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5191 | 5057 | 6078 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5192 | 5058 | 6079 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5193 | 5059 | 6080 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5194 | 5060 | 6081 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5195-3p | 5061 | 6082 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5195-5p | 5062 | 6083 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5196-3p | 5063 | 6084 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5196-5p | 5064 | 6085 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5197-3p | 5065 | 6086 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-5197-5p | 5066 | 6087 | discovered in lymphoblastic leukaemia | | |
| hsa-miR-519a-3p | 5067 | 6088 | placenta | HCC | |
| hsa-miR-519a-5p | 5068 | 6089 | placenta | HCC | |
| hsa-miR-519b-3p | 5069 | 6090 | | breast cancer | |
| hsa-miR-519b-5p | 5070 | 6091 | | breast cancer | |

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|---|---|---|---|---|---|
| hsa-miR-519c-3p | 5071 | 6092 | | | |
| hsa-miR-519c-5p | 5072 | 6093 | | | |
| hsa-miR-519d | 5073 | 6094 | placenta | | |
| hsa-miR-519e-3p | 5074 | 6095 | placenta | | |
| hsa-miR-519e-5p | 5075 | 6096 | placenta | | |
| hsa-miR-520a-3p | 5076 | 6097 | placenta | | |
| hsa-miR-520a-5p | 5077 | 6098 | placenta | | |
| hsa-miR-520b | 5078 | 6099 | | breast cancer | |
| hsa-miR-520c-3p | 5079 | 6100 | | gastric cancer, breast tumor | |
| hsa-miR-520c-5p | 5080 | 6101 | | breast tumor | |
| hsa-miR-520d-3p | 5081 | 6102 | | various cancer cells | |
| hsa-miR-520d-5p | 5082 | 6103 | | various cancer cells | |
| hsa-miR-520e | 5083 | 6104 | | hepatoma | tomor suppressor |
| hsa-miR-520f | 5084 | 6105 | | breast cancer | |
| hsa-miR-520g | 5085 | 6106 | | HCC, bladder cancer, breast cancer | |
| hsa-miR-520h | 5086 | 6107 | placental specific | | |
| hsa-miR-521 | 5087 | 6108 | | prostate cancer | |
| hsa-miR-522-3p | 5088 | 6109 | | HCC | |
| hsa-miR-522-5p | 5089 | 6110 | | HCC | |
| hsa-miR-523-3p | 5090 | 6111 | | | |
| hsa-miR-523-5p | 5091 | 6112 | | | |
| hsa-miR-524-3p | 5092 | 6113 | | colon cancer stem cells | |
| hsa-miR-524-5p | 5093 | 6114 | placental specific | gliomas | |
| hsa-miR-525-3p | 5094 | 6115 | placental specific | HCC | |
| hsa-miR-525-5p | 5095 | 6116 | placental specific | | |
| hsa-miR-526a | 5096 | 6117 | placental specific | | |
| hsa-miR-526b-3p | 5097 | 6118 | placental specific | | |
| hsa-miR-526b-5p | 5098 | 6119 | placental specific | | |
| hsa-miR-527 | 5099 | 6120 | | | |
| hsa-miR-532-3p | 5100 | 6121 | | ALL | |
| hsa-miR-532-5p | 5101 | 6122 | | ALL | |
| hsa-miR-539-3p | 5102 | 6123 | | | |
| hsa-miR-539-5p | 5103 | 6124 | | | |
| hsa-miR-541-3p | 5104 | 6125 | | | |
| hsa-miR-541-5p | 5105 | 6126 | | | |
| hsa-miR-542-3p | 5106 | 6127 | monocytes | | |
| hsa-miR-542-5p | 5107 | 6128 | | basal cell carcinoma, neuroblastoma | |
| hsa-miR-543 | 5108 | 6129 | | | |
| hsa-miR-544a | 5109 | 6130 | | osteocarcoma | |
| hsa-miR-544b | 5110 | 6131 | | osteocarcoma | |
| hsa-miR-545-3p | 5111 | 6132 | | | |
| hsa-miR-545-5p | 5112 | 6133 | | rectal cancer | |
| hsa-miR-548 | 5113 | 6134 | | | |
| hsa-miR-548-3p | 5114 | 6135 | | | |
| hsa-miR-548-5p | 5115 | 6136 | | | |

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|---|---|---|---|---|---|
| hsa-miR-548a | 5116 | 6137 | identified in colorectal microRNAome | | |
| hsa-miR-548a-3p | 5117 | 6138 | identified in colorectal microRNAome | | |
| hsa-miR-548a-5p | 5118 | 6139 | identified in colorectal microRNAome | | |
| hsa-miR-548aa | 5119 | 6140 | identified in cervical tumor | | |
| hsa-miR-548ab | 5120 | 6141 | discovered in B-cells | | |
| hsa-miR-548ac | 5121 | 6142 | discovered in B-cells | | |
| hsa-miR-548ad | 5122 | 6143 | discovered in B-cells | | |
| hsa-miR-548ae | 5123 | 6144 | discovered in B-cells | | |
| hsa-miR-548ag | 5124 | 6145 | discovered in B-cells | | |
| hsa-miR-548ah-3p | 5125 | 6146 | discovered in B-cells | | |
| hsa-miR-548ah-5p | 5126 | 6147 | discovered in B-cells | | |
| hsa-miR-548ai | 5127 | 6148 | discovered in B-cells | | |
| hsa-miR-548aj-3p | 5128 | 6149 | discovered in B-cells | | |
| hsa-miR-548aj-5p | 5129 | 6150 | discovered in B-cells | | |
| hsa-miR-548ak | 5130 | 6151 | discovered in B-cells | | |
| hsa-miR-548al | 5131 | 6152 | discovered in B-cells | | |
| hsa-miR-548am-3p | 5132 | 6153 | discovered in B-cells | | |
| hsa-miR-548am-5p | 5133 | 6154 | discovered in B-cells | | |
| hsa-miR-548an | 5134 | 6155 | discovered in B-cells | | |
| hsa-miR-548ao-3p | 5135 | 6156 | | | |
| hsa-miR-548ao-5p | 5136 | 6157 | | | |
| hsa-miR-548ap-3p | 5137 | 6158 | | | |
| hsa-miR-548ap-5p | 5138 | 6159 | | | |
| hsa-miR-548aq-3p | 5139 | 6160 | | | |
| hsa-miR-548aq-5p | 5140 | 6161 | | | |
| hsa-miR-548ar-3p | 5141 | 6162 | | | |
| hsa-miR-548ar-5p | 5142 | 6163 | | | |
| hsa-miR-548as-3p | 5143 | 6164 | | | |
| hsa-miR-548as-5p | 5144 | 6165 | | | |
| hsa-miR-548at-3p | 5145 | 6166 | | prostate cancer | |
| hsa-miR-548at-5p | 5146 | 6167 | | prostate cancer | |
| hsa-miR-548au-3p | 5147 | 6168 | | | |

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|---|---|---|---|---|---|
| hsa-miR-548au-5p | 5148 | 6169 | | | |
| hsa-miR-548av-3p | 5149 | 6170 | | | |
| hsa-miR-548av-5p | 5150 | 6171 | | | |
| hsa-miR-548aw | 5151 | 6172 | | prostate cancer | |
| hsa-miR-548ay-3p | 5152 | 6173 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-548ay-5p | 5153 | 6174 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-548az-3p | 5154 | 6175 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-548az-5p | 5155 | 6176 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-548b-3p | 5156 | 6177 | identified in colorectal microRNAome | | |
| hsa-miR-548b-5p | 5157 | 6178 | immune cells, frontal cortex | | |
| hsa-miR-548c-3p | 5158 | 6179 | identified in colorectal microRNAome | | |
| hsa-miR-548c-5p | 5159 | 6180 | immune cells, frontal cortex | | |
| hsa-miR-548d-3p | 5160 | 6181 | identified in colorectal microRNAome | | |
| hsa-miR-548d-5p | 5161 | 6182 | identified in colorectal microRNAome | | |
| hsa-miR-548e | 5162 | 6183 | embryonic stem cells | | |
| hsa-miR-548f | 5163 | 6184 | embryonic stem cells | | |
| hsa-miR-548g-3p | 5164 | 6185 | embryonic stem cells | | |
| hsa-miR-548g-5p | 5165 | 6186 | embryonic stem cells | | |
| hsa-miR-548h-3p | 5166 | 6187 | embryonic stem cells | | |
| hsa-miR-548h-5p | 5167 | 6188 | embryonic stem cells | | |
| hsa-miR-548i | 5168 | 6189 | embryonic stem cells, immune cells | | |
| hsa-miR-548j | 5169 | 6190 | immune cells | | |
| hsa-miR-548k | 5170 | 6191 | embryonic stem cells | | |
| hsa-miR-548l | 5171 | 6192 | embryonic stem cells | | |
| hsa-miR-548m | 5172 | 6193 | embryonic stem cells | | |
| hsa-miR-548n | 5173 | 6194 | embryonic stem cells, immune cells | | |

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|---|---|---|---|---|---|
| hsa-miR-548o-3p | 5174 | 6195 | embryonic stem cells | | |
| hsa-miR-548o-5p | 5175 | 6196 | embryonic stem cells | | |
| hsa-miR-548p | 5176 | 6197 | embryonic stem cells | | |
| hsa-miR-548q | 5177 | 6198 | | ovarian cancer cells | |
| hsa-miR-548s | 5178 | 6199 | discovered in the melanoma MicroRNAome | | |
| hsa-miR-548t-3p | 5179 | 6200 | discovered in the melanoma MicroRNAome | | |
| hsa-miR-548t-5p | 5180 | 6201 | discovered in the melanoma MicroRNAome | | |
| hsa-miR-548u | 5181 | 6202 | discovered in the melanoma MicroRNAome | | |
| hsa-miR-548w | 5182 | 6203 | discovered in the melanoma MicroRNAome | | |
| hsa-miR-548y | 5183 | 6204 | | | |
| hsa-miR-548z | 5184 | 6205 | discovered in cervical tumor | | |
| hsa-miR-549a | 5185 | 6206 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-550a-3-5p | 5186 | 6207 | | Hepatocellular Carcinoma | |
| hsa-miR-550a-3p | 5187 | 6208 | | Hepatocellular Carcinoma | |
| hsa-miR-550a-5p | 5188 | 6209 | | Hepatocellular Carcinoma | |
| hsa-miR-550b-2-5p | 5189 | 6210 | discovered in cervical tumor | | |
| hsa-miR-550b-3p | 5190 | 6211 | discovered in cervical tumor | | |
| hsa-miR-551a | 5191 | 6212 | | gastric cancer | |
| hsa-miR-551b-3p | 5192 | 6213 | hepatocytes | | |
| hsa-miR-551b-5p | 5193 | 6214 | hepatocytes | | |
| hsa-miR-552 | 5194 | 6215 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-553 | 5195 | 6216 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-554 | 5196 | 6217 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-555 | 5197 | 6218 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-556-3p | 5198 | 6219 | discovered in a | | |

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|---|---|---|---|---|---|
| | | | colorectal MicroRNAome | | |
| hsa-miR-556-5p | 5199 | 6220 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-557 | 5200 | 6221 | liver(hepatocytes) | | |
| hsa-miR-5571-3p | 5201 | 6222 | discoveredd in Salivary gland | | |
| hsa-miR-5571-5p | 5202 | 6223 | discoveredd in Salivary gland | | |
| hsa-miR-5572 | 5203 | 6224 | discoveredd in Salivary gland | | |
| hsa-miR-5579-3p | 5204 | 6225 | | | |
| hsa-miR-5579-5p | 5205 | 6226 | | | |
| hsa-miR-558 | 5206 | 6227 | | neuroblastoma | |
| hsa-miR-5580-3p | 5207 | 6228 | | | |
| hsa-miR-5580-5p | 5208 | 6229 | | | |
| hsa-miR-5581-3p | 5209 | 6230 | | | |
| hsa-miR-5581-5p | 5210 | 6231 | | | |
| hsa-miR-5582-3p | 5211 | 6232 | | | |
| hsa-miR-5582-5p | 5212 | 6233 | | | |
| hsa-miR-5583-3p | 5213 | 6234 | | | |
| hsa-miR-5583-5p | 5214 | 6235 | | | |
| hsa-miR-5584-3p | 5215 | 6236 | | | |
| hsa-miR-5584-5p | 5216 | 6237 | | | |
| hsa-miR-5585-3p | 5217 | 6238 | | | |
| hsa-miR-5585-5p | 5218 | 6239 | | | |
| hsa-miR-5586-3p | 5219 | 6240 | | | |
| hsa-miR-5586-5p | 5220 | 6241 | | | |
| hsa-miR-5587-3p | 5221 | 6242 | | | |
| hsa-miR-5587-5p | 5222 | 6243 | | | |
| hsa-miR-5588-3p | 5223 | 6244 | | | |
| hsa-miR-5588-5p | 5224 | 6245 | | | |
| hsa-miR-5589-3p | 5225 | 6246 | | | |
| hsa-miR-5589-5p | 5226 | 6247 | | | |
| hsa-miR-559 | 5227 | 6248 | | | |
| hsa-miR-5590-3p | 5228 | 6249 | | | |
| hsa-miR-5590-5p | 5229 | 6250 | | | |
| hsa-miR-5591-3p | 5230 | 6251 | | | |
| hsa-miR-5591-5p | 5231 | 6252 | | | |
| hsa-miR-561-3p | 5232 | 6253 | | multiple myeloma | |
| hsa-miR-561-5p | 5233 | 6254 | | multiple myeloma | |
| hsa-miR-562 | 5234 | 6255 | | | |
| hsa-miR-563 | 5235 | 6256 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-564 | 5236 | 6257 | | Chronic myeloid leukemia | |
| hsa-miR-566 | 5237 | 6258 | | MALT lymphoma/lymphocyte | |
| hsa-miR-567 | 5238 | 6259 | | colorectal cancer | |
| hsa-miR-568 | 5239 | 6260 | discovered in a colorectal | | |

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|---|---|---|---|---|---|
| | | | MicroRNAome | | |
| hsa-miR-5680 | 5240 | 6261 | | Associated with metastatic prostate cancer | |
| hsa-miR-5681a | 5241 | 6262 | | Associated with metastatic prostate cancer | |
| hsa-miR-5681b | 5242 | 6263 | | Associated with metastatic prostate cancer | |
| hsa-miR-5682 | 5243 | 6264 | | Associated with metastatic prostate cancer | |
| hsa-miR-5683 | 5244 | 6265 | | Associated with metastatic prostate cancer | |
| hsa-miR-5684 | 5245 | 6266 | | Associated with metastatic prostate cancer | |
| hsa-miR-5685 | 5246 | 6267 | | Associated with metastatic prostate cancer | |
| hsa-miR-5686 | 5247 | 6268 | | Associated with metastatic prostate cancer | |
| hsa-miR-5687 | 5248 | 6269 | | Associated with metastatic prostate cancer | |
| hsa-miR-5688 | 5249 | 6270 | | Associated with metastatic prostate cancer | |
| hsa-miR-5689 | 5250 | 6271 | | Associated with metastatic prostate cancer | |
| hsa-miR-569 | 5251 | 6272 | | | |
| hsa-miR-5690 | 5252 | 6273 | | Associated with metastatic prostate cancer | |
| hsa-miR-5691 | 5253 | 6274 | | Associated with metastatic prostate cancer | |
| hsa-miR-5692a | 5254 | 6275 | | Associated with metastatic prostate cancer | |
| hsa-miR-5692b | 5255 | 6276 | | Associated with metastatic prostate cancer | |
| hsa-miR-5692c | 5256 | 6277 | | Associated with metastatic prostate cancer | |
| hsa-miR-5693 | 5257 | 6278 | | Associated with metastatic prostate cancer | |
| hsa-miR-5694 | 5258 | 6279 | | Associated with metastatic | |

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|---|---|---|---|---|---|
| | | | | prostate cancer | |
| hsa-miR-5695 | 5259 | 6280 | | Associated with metastatic prostate cancer | |
| hsa-miR-5696 | 5260 | 6281 | | Associated with metastatic prostate cancer | |
| hsa-miR-5697 | 5261 | 6282 | | Associated with metastatic prostate cancer | |
| hsa-miR-5698 | 5262 | 6283 | | Associated with metastatic prostate cancer | |
| hsa-miR-5699 | 5263 | 6284 | | Associated with metastatic prostate cancer | |
| hsa-miR-5700 | 5264 | 6285 | | Associated with metastatic prostate cancer | |
| hsa-miR-5701 | 5265 | 6286 | | Associated with metastatic prostate cancer | |
| hsa-miR-5702 | 5266 | 6287 | | Associated with metastatic prostate cancer | |
| hsa-miR-5703 | 5267 | 6288 | | Associated with metastatic prostate cancer | |
| hsa-miR-570-3p | 5268 | 6289 | | follicular lymphoma | |
| hsa-miR-5704 | 5269 | 6290 | | Associated with metastatic prostate cancer | |
| hsa-miR-5705 | 5270 | 6291 | | Associated with metastatic prostate cancer | |
| hsa-miR-570-5p | 5271 | 6292 | | follicular lymphoma | |
| hsa-miR-5706 | 5272 | 6293 | | Associated with metastatic prostate cancer | |
| hsa-miR-5707 | 5273 | 6294 | | Associated with metastatic prostate cancer | |
| hsa-miR-5708 | 5274 | 6295 | | Associated with metastatic prostate cancer | |
| hsa-miR-571 | 5275 | 6296 | frontal cortex | | |
| hsa-miR-572 | 5276 | 6297 | circulating microRNA (in plasma) | basal cell carcinoma | |
| hsa-miR-573 | 5277 | 6298 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-5739 | 5278 | 6299 | endothelial cells | | |

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|---|---|---|---|---|---|
| hsa-miR-574-3p | 5279 | 6300 | blood (myeloid cells) | follicular lymphoma | |
| hsa-miR-574-5p | 5280 | 6301 | semen | | |
| hsa-miR-575 | 5281 | 6302 | | gastric cancer | |
| hsa-miR-576-3p | 5282 | 6303 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-576-5p | 5283 | 6304 | cartilage/ chondrocyte | | |
| hsa-miR-577 | 5284 | 6305 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-578 | 5285 | 6306 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-5787 | 5286 | 6307 | fibroblast | | |
| hsa-miR-579 | 5287 | 6308 | | | |
| hsa-miR-580 | 5288 | 6309 | | breast cancer | |
| hsa-miR-581 | 5289 | 6310 | liver(hepatocytes) | | |
| hsa-miR-582-3p | 5290 | 6311 | cartilage/chondrocyte | bladder cancer | |
| hsa-miR-582-5p | 5291 | 6312 | | bladder cancer | |
| hsa-miR-583 | 5292 | 6313 | | rectal cancer cells | |
| hsa-miR-584-3p | 5293 | 6314 | | tumor cells (follicular lymphoma, rectal cancer cells) | |
| hsa-miR-584-5p | 5294 | 6315 | | tumor cells (follicular lymphoma, rectal cancer cells) | |
| hsa-miR-585 | 5295 | 6316 | | oral squamous cell carcinoma | |
| hsa-miR-586 | 5296 | 6317 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-587 | 5297 | 6318 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-588 | 5298 | 6319 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-589-3p | 5299 | 6320 | mesothelial cells | | |
| hsa-miR-589-5p | 5300 | 6321 | mesothelial cells | | |
| hsa-miR-590-3p | 5301 | 6322 | cardiomyocytes | | Cell cycle progression |
| hsa-miR-590-5p | 5302 | 6323 | cardiomyocytes | | Cell cycle progression |
| hsa-miR-591 | 5303 | 6324 | | neuroblastoma | |
| hsa-miR-592 | 5304 | 6325 | | hepatocellular carcinoma | |
| hsa-miR-593-3p | 5305 | 6326 | | esophageal cancer | |
| hsa-miR-593-5p | 5306 | 6327 | | esophageal cancer | |
| hsa-miR-595 | 5307 | 6328 | | heart failure | |
| hsa-miR-596 | 5308 | 6329 | | ependymoma, | |

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|---|---|---|---|---|---|
| | | | | cancers | |
| hsa-miR-597 | 5309 | 6330 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-598 | 5310 | 6331 | Blood (lymphocytes) | | |
| hsa-miR-599 | 5311 | 6332 | | Multiple sclerosis | |
| hsa-miR-600 | 5312 | 6333 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-601 | 5313 | 6334 | | various cancers ( colonrectal, gastric) | |
| hsa-miR-602 | 5314 | 6335 | oocyte | | |
| hsa-miR-603 | 5315 | 6336 | | | |
| hsa-miR-604 | 5316 | 6337 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-605 | 5317 | 6338 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-606 | 5318 | 6339 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-6068 | 5319 | 6340 | discovered in endothelial cells | | |
| hsa-miR-6069 | 5320 | 6341 | discovered in endothelial cells | | |
| hsa-miR-607 | 5321 | 6342 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-6070 | 5322 | 6343 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-6071 | 5323 | 6344 | discovered in endothelial cells | | |
| hsa-miR-6072 | 5324 | 6345 | discovered in endothelial cells | | |
| hsa-miR-6073 | 5325 | 6346 | discovered in endothelial cells | | |
| hsa-miR-6074 | 5326 | 6347 | discovered in endothelial cells | | |
| hsa-miR-6075 | 5327 | 6348 | discovered in endothelial cells | | |
| hsa-miR-6076 | 5328 | 6349 | discovered in endothelial cells | | |
| hsa-miR-6077 | 5329 | 6350 | discovered in endothelial cells | | |
| hsa-miR-6078 | 5330 | 6351 | discovered in endothelial cells | | |
| hsa-miR-6079 | 5331 | 6352 | discovered in endothelial cells | | |
| hsa-miR-608 | 5332 | 6353 | | various cancers | |
| hsa-miR-6080 | 5333 | 6354 | discovered in endothelial cells | | |

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| hsa-miR-6081 | 5334 | 6355 | discovered in endothelial cells | | |
| hsa-miR-6082 | 5335 | 6356 | discovered in endothelial cells | | |
| hsa-miR-6083 | 5336 | 6357 | discovered in endothelial cells | | |
| hsa-miR-6084 | 5337 | 6358 | discovered in endothelial cells | | |
| hsa-miR-6085 | 5338 | 6359 | discovered in endothelial cells | | |
| hsa-miR-6086 | 5339 | 6360 | embryonic stem cells | | |
| hsa-miR-6087 | 5340 | 6361 | embryonic stem cells | | |
| hsa-miR-6088 | 5341 | 6362 | embryonic stem cells | | |
| hsa-miR-6089 | 5342 | 6363 | embryonic stem cells | | |
| hsa-miR-609 | 5343 | 6364 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-6090 | 5344 | 6365 | embryonic stem cells | | |
| hsa-miR-610 | 5345 | 6366 | | gastric cancer | |
| hsa-miR-611 | 5346 | 6367 | | Renal cell carcinoma | |
| hsa-miR-612 | 5347 | 6368 | | AM leukemia | |
| hsa-miR-6124 | 5348 | 6369 | | | |
| hsa-miR-6125 | 5349 | 6370 | | | |
| hsa-miR-6126 | 5350 | 6371 | | | |
| hsa-miR-6127 | 5351 | 6372 | | | |
| hsa-miR-6128 | 5352 | 6373 | | | |
| hsa-miR-6129 | 5353 | 6374 | | | |
| hsa-miR-613 | 5354 | 6375 | lipid metabollism | | |
| hsa-miR-6130 | 5355 | 6376 | | | |
| hsa-miR-6131 | 5356 | 6377 | | | |
| hsa-miR-6132 | 5357 | 6378 | | | |
| hsa-miR-6133 | 5358 | 6379 | | | |
| hsa-miR-6134 | 5359 | 6380 | | | |
| hsa-miR-614 | 5360 | 6381 | circulating micrRNAs (in Plasma) | | |
| hsa-miR-615-3p | 5361 | 6382 | | | |
| hsa-miR-615-5p | 5362 | 6383 | | | |
| hsa-miR-616-3p | 5363 | 6384 | | prostate cancer | |
| hsa-miR-6165 | 5364 | 6385 | | | Pro-apoptotic factor |
| hsa-miR-616-5p | 5365 | 6386 | | prostate cancer | |
| hsa-miR-617 | 5366 | 6387 | | | |
| hsa-miR-618 | 5367 | 6388 | | | |
| hsa-miR-619 | 5368 | 6389 | discovered in a colorectal MicroRNAome | | |
| hsa-miR-620 | 5369 | 6390 | discovered in a | | |

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|---|---|---|---|---|---|
| | | | colorectal MicroRNAome | | |
| hsa-miR-621 | 5370 | 6391 | | | |
| hsa-miR-622 | 5371 | 6392 | | | |
| hsa-miR-623 | 5372 | 6393 | | | |
| hsa-miR-624-3p | 5373 | 6394 | chondrocyte | | |
| hsa-miR-624-5p | 5374 | 6395 | chondrocyte | | |
| hsa-miR-625-3p | 5375 | 6396 | liver(hepatocytes),circulating (blood) | various cancers | |
| hsa-miR-625-5p | 5376 | 6397 | liver(hepatocytes),circulating (blood) | various cancers | |
| hsa-miR-626 | 5377 | 6398 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-627 | 5378 | 6399 | | colorectal cancer | |
| hsa-miR-628-3p | 5379 | 6400 | | neuroblastoma | |
| hsa-miR-628-5p | 5380 | 6401 | | neuroblastoma | |
| hsa-miR-629-3p | 5381 | 6402 | | B-lineage ALL, T cell lupus, RCC/kidney | |
| hsa-miR-629-5p | 5382 | 6403 | | B-lineage ALL, T cell lupus, RCC/kidney | |
| hsa-miR-630 | 5383 | 6404 | chondrocytes | rectal cancer | |
| hsa-miR-631 | 5384 | 6405 | discovered in the colorectal MicroRNAom | | |
| hsa-miR-632 | 5385 | 6406 | | myelodysplastic syndromes | |
| hsa-miR-633 | 5386 | 6407 | | multiple sclerosis | |
| hsa-miR-634 | 5387 | 6408 | cartilage/ chondrocyte | | |
| hsa-miR-635 | 5388 | 6409 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-636 | 5389 | 6410 | | myelodysplastic syndromes | |
| hsa-miR-637 | 5390 | 6411 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-638 | 5391 | 6412 | | Lupus nephritis, basal cell carcinoma | |
| hsa-miR-639 | 5392 | 6413 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-640 | 5393 | 6414 | | Chronic lymphocytic leukemia | |
| hsa-miR-641 | 5394 | 6415 | cartilage/ chondrocyte | | |
| hsa-miR-642a-3p | 5395 | 6416 | adipocyte | | |
| hsa-miR-642a-5p | 5396 | 6417 | discovered in the colorectal MicroRNAome | | |

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|---|---|---|---|---|---|
| hsa-miR-642b-3p | 5397 | 6418 | discovered in a cervial tumo | | |
| hsa-miR-642b-5p | 5398 | 6419 | discovered in a cervial tumo | | |
| hsa-miR-643 | 5399 | 6420 | discovered in the colorectal MicroRNAome | | |
| hsa-miR-644a | 5400 | 6421 | | | |
| hsa-miR-645 | 5401 | 6422 | | ovarian cancer | |
| hsa-miR-646 | 5402 | 6423 | | | |
| hsa-miR-647 | 5403 | 6424 | | prostate and lung cancer | |
| hsa-miR-648 | 5404 | 6425 | circulating micrRNAs (in Plasma) | | |
| hsa-miR-649 | 5405 | 6426 | Serum | | |
| hsa-miR-6499-3p | 5406 | 6427 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6499-5p | 5407 | 6428 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-650 | 5408 | 6429 | | melanoma | |
| hsa-miR-6500-3p | 5409 | 6430 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6500-5p | 5410 | 6431 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6501-3p | 5411 | 6432 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6501-5p | 5412 | 6433 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6502-3p | 5413 | 6434 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6502-5p | 5414 | 6435 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6503-3p | 5415 | 6436 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6503-5p | 5416 | 6437 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6504-3p | 5417 | 6438 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6504-5p | 5418 | 6439 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6505-3p | 5419 | 6440 | discovered in abnormal skin | | |

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|---|---|---|---|---|---|
| | | | (psoriasis) | | |
| hsa-miR-6505-5p | 5420 | 6441 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6506-3p | 5421 | 6442 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6506-5p | 5422 | 6443 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6507-3p | 5423 | 6444 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6507-5p | 5424 | 6445 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6508-3p | 5425 | 6446 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6508-5p | 5426 | 6447 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6509-3p | 5427 | 6448 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6509-5p | 5428 | 6449 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-651 | 5429 | 6450 | discovered in the colorectal MicroRNAome | lung cancer | |
| hsa-miR-6510-3p | 5430 | 6451 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6510-5p | 5431 | 6452 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6511a-3p | 5432 | 6453 | discovered in abnormal skin (psoriasis) and epididymis | | |
| hsa-miR-6511a-5p | 5433 | 6454 | discovered in abnormal skin (psoriasis) and epididymis | | |
| hsa-miR-6511b-3p | 5434 | 6455 | discovered in epididymis | | |
| hsa-miR-6511b-5p | 5435 | 6456 | discovered in epididymis | | |
| hsa-miR-6512-3p | 5436 | 6457 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6512-5p | 5437 | 6458 | discovered in abnormal skin (psoriasis) | | |

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|---|---|---|---|---|---|
| hsa-miR-6513-3p | 5438 | 6459 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6513-5p | 5439 | 6460 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6514-3p | 5440 | 6461 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6514-5p | 5441 | 6462 | discovered in abnormal skin (psoriasis) | | |
| hsa-miR-6515-3p | 5442 | 6463 | discovered in abnormal skin (psoriasis) and epididymis | | |
| hsa-miR-6515-5p | 5443 | 6464 | discovered in abnormal skin (psoriasis) and epididymis | | |
| hsa-miR-652-3p | 5444 | 6465 | | rectal cancer cells | |
| hsa-miR-652-5p | 5445 | 6466 | | rectal cancer cells | |
| hsa-miR-653 | 5446 | 6467 | Discovered in the colorectal MicroRNAome | | |
| hsa-miR-654-3p | 5447 | 6468 | Discovered in the colorectal MicroRNAome | | |
| hsa-miR-654-5p | 5448 | 6469 | bone marrow | prostate cancer | |
| hsa-miR-655 | 5449 | 6470 | | | |
| hsa-miR-656 | 5450 | 6471 | | various cancers | |
| hsa-miR-657 | 5451 | 6472 | oligodendrocytes | diabetes | |
| hsa-miR-658 | 5452 | 6473 | | gastric cancer | |
| hsa-miR-659-3p | 5453 | 6474 | myoblast | | |
| hsa-miR-659-5p | 5454 | 6475 | myoblast | | |
| hsa-miR-660-3p | 5455 | 6476 | myoblast | | |
| hsa-miR-660-5p | 5456 | 6477 | myoblast | | |
| hsa-miR-661 | 5457 | 6478 | | breast cancer | |
| hsa-miR-662 | 5458 | 6479 | endothelial progenitor cells, oocytes | | |
| hsa-miR-663a | 5459 | 6480 | | follicular lymphoma, Lupus nephritis | |
| hsa-miR-663b | 5460 | 6481 | | follicular lymphoma, Lupus nephritis | |
| hsa-miR-664a-3p | 5461 | 6482 | embryonic stem cells | | component of SnoRNAs |
| hsa-miR-664a-5p | 5462 | 6483 | embryonic stem cells | | component of SnoRNAs |
| hsa-miR-664b-3p | 5463 | 6484 | embryonic stem cells | | component of SnoRNAs |
| hsa-miR-664b-5p | 5464 | 6485 | embryonic stem cells | | component of SnoRNAs |

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|---|---|---|---|---|---|
| hsa-miR-665 | 5465 | 6486 | | breast cancer | |
| hsa-miR-668 | 5466 | 6487 | keratinocytes | | senescence |
| hsa-miR-670 | 5467 | 6488 | | | |
| hsa-miR-671-3p | 5468 | 6489 | | | |
| hsa-miR-6715a-3p | 5469 | 6490 | discovered in epididymis | | |
| hsa-miR-6715b-3p | 5470 | 6491 | discovered in epididymis | | |
| hsa-miR-6715b-5p | 5471 | 6492 | discovered in epididymis | | |
| hsa-miR-671-5p | 5472 | 6493 | | rectal cancer, prolactinomas | |
| hsa-miR-6716-3p | 5473 | 6494 | discovered in epididymis | | |
| hsa-miR-6716-5p | 5474 | 6495 | discovered in epididymis | | |
| hsa-miR-6717-5p | 5475 | 6496 | discovered in epididymis | | |
| hsa-miR-6718-5p | 5476 | 6497 | discovered in epididymis | | |
| hsa-miR-6719-3p | 5477 | 6498 | discovered in epididymis | | |
| hsa-miR-6720-3p | 5478 | 6499 | discovered in epididymis | | |
| hsa-miR-6721-5p | 5479 | 6500 | discovered in epididymis | | |
| hsa-miR-6722-3p | 5480 | 6501 | discovered in epididymis | | |
| hsa-miR-6722-5p | 5481 | 6502 | discovered in epididymis | | |
| hsa-miR-6723-5p | 5482 | 6503 | discovered in epididymis | | |
| hsa-miR-6724-5p | 5483 | 6504 | discovered in epididymis | | |
| hsa-miR-675-3p | 5484 | 6505 | | adrenocortical tumor | |
| hsa-miR-675-5p | 5485 | 6506 | | adrenocortical tumor | |
| hsa-miR-676-3p | 5486 | 6507 | discovered in female reproductuve tract | | |
| hsa-miR-676-5p | 5487 | 6508 | discovered in female reproductuve tract | | |
| hsa-miR-708-3p | 5488 | 6509 | | Various cancers ( lung, bladder, pancreatic , ALL) | |
| hsa-miR-708-5p | 5489 | 6510 | | Various cancers ( lung, bladder, pancreatic , ALL) | |
| hsa-miR-711 | 5490 | 6511 | | cutaneous T-cell lymphomas | |
| hsa-miR-7-1-3p | 5491 | 6512 | Glioblast, brain, prancreas | | |
| hsa-miR-718 | 5492 | 6513 | blood | | |

| | | | | | |
|---|---|---|---|---|---|
| hsa-miR-7-2-3p | 5493 | 6514 | brain, pancreas | | |
| hsa-miR-744-3p | 5494 | 6515 | heart | | |
| hsa-miR-744-5p | 5495 | 6516 | embryonic stem cells, heart | | |
| hsa-miR-758-3p | 5496 | 6517 | cholesterol regulation and brain | | |
| hsa-miR-758-5p | 5497 | 6518 | cholesterol regulation and brain | | |
| hsa-miR-759 | 5498 | 6519 | | | |
| hsa-miR-7-5p | 5499 | 6520 | brain | | |
| hsa-miR-760 | 5500 | 6521 | | colonrectal and breast cancer | |
| hsa-miR-761 | 5501 | 6522 | | | |
| hsa-miR-762 | 5502 | 6523 | corneal epithelial cells | | |
| hsa-miR-764 | 5503 | 6524 | osteoblast | | |
| hsa-miR-765 | 5504 | 6525 | | rectal cancer | |
| hsa-miR-766-3p | 5505 | 6526 | embryonic stem cells | | |
| hsa-miR-766-5p | 5506 | 6527 | embryonic stem cells | | |
| hsa-miR-767-3p | 5507 | 6528 | / | | |
| hsa-miR-767-5p | 5508 | 6529 | / | | |
| hsa-miR-769-3p | 5509 | 6530 | | | |
| hsa-miR-769-5p | 5510 | 6531 | | | |
| hsa-miR-770-5p | 5511 | 6532 | | | |
| hsa-miR-802 | 5512 | 6533 | brain , epithelial cells, hepatocytes | down symdrome | |
| hsa-miR-873-3p | 5513 | 6534 | | | |
| hsa-miR-873-5p | 5514 | 6535 | | | |
| hsa-miR-874 | 5515 | 6536 | | cervical cancer, lung cancer, carcinoma | |
| hsa-miR-875-3p | 5516 | 6537 | | | |
| hsa-miR-875-5p | 5517 | 6538 | | | |
| hsa-miR-876-3p | 5518 | 6539 | | | |
| hsa-miR-876-5p | 5519 | 6540 | | | |
| hsa-miR-877-3p | 5520 | 6541 | | | |
| hsa-miR-877-5p | 5521 | 6542 | | | |
| hsa-miR-885-3p | 5522 | 6543 | embryonic stem cells | | |
| hsa-miR-885-5p | 5523 | 6544 | embryonic stem cells | | |
| hsa-miR-887 | 5524 | 6545 | | | |
| hsa-miR-888-3p | 5525 | 6546 | | | |
| hsa-miR-888-5p | 5526 | 6547 | | | |
| hsa-miR-889 | 5527 | 6548 | | | |
| hsa-miR-890 | 5528 | 6549 | epididymis | | |
| hsa-miR-891a | 5529 | 6550 | epididymis | osteosarcoma | |
| hsa-miR-891b | 5530 | 6551 | epididymis | | |
| hsa-miR-892a | 5531 | 6552 | epididymis | | |
| hsa-miR-892b | 5532 | 6553 | epididymis | | |
| hsa-miR-892c-3p | 5533 | 6554 | discovered in epididymis | | |

| | | | | | |
|---|---|---|---|---|---|
| hsa-miR-892c-5p | 5534 | 6555 | discovered in epididymis | | |
| hsa-miR-920 | 5535 | 6556 | human testis | | |
| hsa-miR-921 | 5536 | 6557 | human testis | muscle invasive bladder cancer | |
| hsa-miR-922 | 5537 | 6558 | human testis, neuronal tissues | multiple sclerosis, Alcoholic liver disease | |
| hsa-miR-924 | 5538 | 6559 | human testis | | |
| hsa-miR-92a-1-5p | 5539 | 6560 | endothelial cells | | |
| hsa-miR-92a-2-5p | 5540 | 6561 | endothelial cells | | |
| hsa-miR-92a-3p | 5541 | 6562 | endothelial cells, CNS | | |
| hsa-miR-92b-3p | 5542 | 6563 | endothelial cells, heart | | |
| hsa-miR-92b-5p | 5543 | 6564 | endothelial cells, heart | | |
| hsa-miR-933 | 5544 | 6565 | discovered in cervical cancer | | |
| hsa-miR-93-3p | 5545 | 6566 | embryonic stem cells | basal cell carcinoma | |
| hsa-miR-934 | 5546 | 6567 | discovered in cervical cancer | | |
| hsa-miR-935 | 5547 | 6568 | blood monoclear cells | energy metabolism/ obesity, medullablastoma/ neural stem cells | |
| hsa-miR-93-5p | 5548 | 6569 | embryonic stem cells | | |
| hsa-miR-936 | 5549 | 6570 | skin | | |
| hsa-miR-937-3p | 5550 | 6571 | | cervical cancer | |
| hsa-miR-937-5p | 5551 | 6572 | | cervical cancer | |
| hsa-miR-938 | 5552 | 6573 | | Various cancer cells | |
| hsa-miR-939-3p | 5553 | 6574 | hepatocytes | | |
| hsa-miR-939-5p | 5554 | 6575 | hepatocytes | | |
| hsa-miR-9-3p | 5555 | 6576 | brain | Cancers and brain diseases | |
| hsa-miR-940 | 5556 | 6577 | identified in Cervical cancer | | |
| hsa-miR-941 | 5557 | 6578 | Embryonic stem cells | | |
| hsa-miR-942 | 5558 | 6579 | | lung cancer | |
| hsa-miR-943 | 5559 | 6580 | identified in Cervical cancer | | |
| hsa-miR-944 | 5560 | 6581 | | various cancers (cervical, pancreatic, colonrectal) | |
| hsa-miR-95 | 5561 | 6582 | | various cancers (pancreatic, glioblastoma, colorectal etc) | |
| hsa-miR-9-5p | 5562 | 6583 | brain | Cancers and brain | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | disease | |
| hsa-miR-96-3p | 5563 | 6584 | stem cells | various cancers (prostate, lymphoma, HCC, etc) and inflammation | |
| hsa-miR-96-5p | 5564 | 6585 | stem cells | various cancers (prostate, lymphoma, HCC, etc) and inflammation | |
| hsa-miR-98-3p | 5565 | 6586 | | various cancer cells | apoptosis |
| hsa-miR-98-5p | 5566 | 6587 | | various cancer cells | apoptosis |
| hsa-miR-99a-3p | 5567 | 6588 | hemapoietic cells | | |
| hsa-miR-99a-5p | 5568 | 6589 | hemapoietic cells | | |
| hsa-miR-99b-3p | 5569 | 6590 | hemapoietic cells, embryonic stem cells | | |
| hsa-miR-99b-5p | 5570 | 6591 | hemapoietic cells, embryonic stem cells | | |

**[00339]** MicroRNAs that are enriched in specific types of immune cells are listed in Table 11. Furthermore, novel miroRNAs are discovered in the immune cells in the art through micro-array hybridization and microtome analysis (Jima DD et al, Blood, 2010, 116:e118-e127; Vaz C et al., BMC Genomics, 2010, 11,288, the content of each of which is incorporated herein by reference in its entirety). In Table 11, "HCC" represents hepatocellular carcinoma, "ALL" stands for acute lymphoblastsic leukemia and "CLL" stands for chrominc lymphocytic leukemia.

**Table 11. microRNAs in immune cells**

| **microRNA** | **mir SEQ ID** | **BS SEQ ID** | **tissues/cells with MicroRNAs** | **associated diseases** | **biological functions/targets** |
|---|---|---|---|---|---|
| hsa-let-7a-2-3p | 2508 | 3529 | embryonic stem cells, lung, myeloid cells | inflammatory, various cancers (lung, cervical, breast, pancreatic, etc) | tumor suppressor, target to c-myc |
| hsa-let-7a-3p | 2509 | 3530 | embryonic stem cell, lung, myeloid cells | inflammatory, various cancers (lung, cervical, breast, pancreatic, etc) | tumor suppressor, target to c-myc |
| hsa-let-7a-5p | 2510 | 3531 | embryonic stem cells, lung, | inflammatory, various cancers | tumor suppressor, |

| | | | | | |
|---|---|---|---|---|---|
| | | | myeloid cells | (lung, cervical, breast, pancreatic, etc) | target to c-myc |
| hsa-let-7c | 2513 | 3534 | dendritic cells | various cacners (cervical, pancreatic, lung , esopphageal, etc) | tumor suppressor apoptosis (target to BCL-xl) |
| hsa-let-7e-3p | 2516 | 3537 | immune cells | various cancer cells, autoimmunity TLR signal pathway in endotoxin tolerance | tumor suppressor |
| hsa-let-7e-5p | 2517 | 3538 | immune cells | associated with various cancer cells | tumor suppressor |
| hsa-let-7f-1-3p | 2518 | 3539 | immune cells (T cells) | associated with various cancer cells | tumor suppressor |
| hsa-let-7f-2-3p | 2519 | 3540 | immune cells (T cells) | associated with various cancer cells | tumor suppressor |
| hsa-let-7f-5p | 2520 | 3541 | immune cells (T cells) | associated with various cancer cells | tumor suppressor |
| hsa-let-7g-3p | 2521 | 3542 | hematopoietic cells, adipose, smooth muscle cells | various cancer cells (lung, breast, etc) | tumor suppressor (target to NFkB, LOX1) |
| hsa-let-7g-5p | 2522 | 3543 | hematopoietic cells, adipose, smooth muscle cells | various cancer cells (lung, breast, etc) | tumor suppressor (target to NFkB, LOX1) |
| hsa-let-7i-3p | 2523 | 3544 | immune cells | chronic lymphocyte leukimia | tumor suppressor |
| hsa-let-7i-5p | 2524 | 3545 | immune cells | chronic lymphocyte leukimia | tumor suppressor |
| hsa-miR-10a-3p | 2530 | 3551 | hematopoeitic cells | acute myeoid leukemia | oncogene, cell growth |
| hsa-miR-10a-5p | 2541 | 3562 | hematopoietic cells | acute myeloid leukemia | oncogene, cell growth |
| hsa-miR-1184 | 2551 | 3572 | Hematopoietic cells | downregulated in oral leukoplakia (OLK) | predited in the intron 22 of F8 gene |
| hsa-miR-125b-1-3p | 2616 | 3637 | hematopoietic cells (monocytes), brain (neuron) | various cancer (ALL, prostate, HCC, etc); TLR signal pathway in endotoxin tolerance | oncogene, cell differentiation |
| hsa-miR-125b-2-3p | 2617 | 3638 | hematopoietic cells (monocytes), brain (neuron) | various cancer (ALL, prostate, HCC etc); TLR signal pathway in endotoxin tolerance | oncogene cell differentiation |
| hsa-miR-125b-5p | 2618 | 3639 | hematopoietic cells, brain (neuron) | various cancer (Cutaneous T cell lymphomas, prostate, HCC, etc); TLR signal pathway | oncogene cell differentiation |

| | | | | | |
|---|---|---|---|---|---|
| | | | | in endotoxin tolerance | |
| hsa-miR-1279 | 2652 | 3673 | monocytes | | |
| hsa-miR-130a-3p | 2690 | 3711 | lung, monocytes, vascular endothelial cells | various cancers (basal cell carcinoma, HCC,ovarian, etc), drug resistance | pro-angiogenic |
| hsa-miR-130a-5p | 2691 | 3712 | lung, monocytes, vasscular endothelial cells | various cancers (basal cell carcinoma, HCC,ovarian, etc), drug resistance | pro-angiogenic |
| hsa-miR-132-3p | 2697 | 3718 | brain(neuron), immune cells | | |
| hsa-miR-132-5p | 2699 | 3720 | brain(neuron), immune cells | | |
| hsa-miR-142-3p | 2720 | 3741 | meyloid cells, hematopoiesis, APC cells | | tumor suppressor, immune response |
| hsa-miR-142-5p | 2721 | 3742 | meyloid cells, hematopoiesis, APC cells | | immune response |
| hsa-miR-143-5p | 2723 | 3744 | vascular smooth muscle, T-cells | increased in serum after virus infection | |
| hsa-miR-146a-3p | 2730 | 3751 | immune cells, hematopoiesis,cartilage, | associated with CLL, TLR signal pathway in endotoxin tolerance | |
| hsa-miR-146a-5p | 2731 | 3752 | immune cells, hematopoiesis, cartilage, | associated with CLL, TLR signal pathway in endotoxin tolerance | |
| hsa-miR-146b-3p | 2732 | 3753 | immune cells | cancers (thyroid carcimona) | immune response |
| hsa-miR-146b-5p | 2733 | 3754 | embryoid body cells | thyroid cancer, associated with CLL | tumor invation, migration |
| hsa-miR-147a | 2736 | 3757 | Macrophage | inflammatory response | |
| hsa-miR-147b | 2737 | 3758 | Macrophage | inflammatory response | |
| hsa-miR-148a-3p | 2738 | 3759 | hematopoietic cells | associated with CLL, T-lineage ALL | |
| hsa-miR-148a-5p | 2739 | 3760 | hematopoietic cells | associated with CLL, T-lineage ALL | |
| hsa-miR-150-3p | 2744 | 3765 | hematopoitic cells (lymphoid) | circulating plasma (acute myeloid leukemia) | |
| hsa-miR-150-5p | 2745 | 3766 | hematopoitic cells (lymphoid) | circulating plasma (acute myeloid | |

| | | | | | |
|---|---|---|---|---|---|
| | | | | leukemia) | |
| hsa-miR-151b | 2748 | 3769 | immune cells (B-cells) | | |
| hsa-miR-155-3p | 2756 | 3777 | T/B cells, monocytes,breast | associated with CLL , TLR signal pathway in endotoxin tolerance ; upregulated in B cell lymphoma (CLL) and other cancers (breast, lung, ovarian, cervical, colorectal, prostate) | |
| hsa-miR-155-5p | 2757 | 3778 | T/B cells, monocytes,breast | associated with CLL , TLR signal pathway in endotoxin tolerance , upregulated in B cell lymphoma (CLL) and other cancers (breast, lung, ovarian, cervical, colorectal, prostate) | |
| hsa-miR-15a-3p | 2759 | 3780 | blood, lymphocyte, hematopoietic tissues (spleen) | chronic lymphocytic leukemia | |
| hsa-miR-15a-5p | 2760 | 3781 | blood, lymphocyte, hematopoietic tissues (spleen) | chronic lymphocytic leukemia | |
| hsa-miR-15b-3p | 2761 | 3782 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-15b-5p | 2762 | 3783 | blood, lymphocyte, hematopoietic tissues (spleen) | | cell cycle, proliferation |
| hsa-miR-16-1-3p | 2763 | 3784 | embryonic stem cells, blood, hematopoietic tissues (spleen) | chronic lymphocytic leukemia | |
| hsa-miR-16-2-3p | 2764 | 3785 | blood, lymphocyte, hematopoietic tissues (spleen) | | |
| hsa-miR-16-5p | 2765 | 3786 | blood, lymphocyte, hematopoietic tissues | | |
| hsa-miR-181a-3p | 2769 | 3790 | glioblast, myeloid cells, | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | Embryonic stem cells | | |
| hsa-miR-181a-5p | 2770 | 3791 | glioblast, myeloid cells, Embryonic stem cells | | |
| hsa-miR-182-3p | 2776 | 3797 | immune cells | colonrectal cancer, autoimmne | immune response |
| hsa-miR-182-5p | 2778 | 3799 | lung, immune cells | autoimmune | immune response |
| hsa-miR-197-3p | 2827 | 3848 | blood (myeloid), other tissues | various cancers (thyroid tumor, leukemia, etc) | |
| hsa-miR-197-5p | 2828 | 3849 | blood (myeloid), other tissues | various cancers (thyroid tumor, leukemia, etc) | |
| hsa-miR-21-3p | 2879 | 3099 | glioblast, Blood (meyloid cells), liver, vascular endothelial cells | autoimmune, heart diseases, cancers | |
| hsa-miR-214-3p | 2880 | 3901 | immune cells, pancreas | varioua cancers (melanoma, pancreatic, ovarian) | immune response |
| hsa-miR-214-5p | 2881 | 3902 | immune cells, pancreas | varioua cancers (melanoma, pancreatic, ovarian) | immune response |
| hsa-miR-21-5p | 2883 | 3904 | blood ( myeloid cells), liver, endothelial cells | autoimmune, heart diseases, cancers | |
| hsa-miR-221-3p | 2894 | 3915 | endothelial cells, immune cells | breast cancer,upregulated in thyroid cell transformation induced by HMGA1, TLR signal pathway in endotoxin tolerance, upregulated in T cell ALL | angiogenesis/vasculogenesis |
| hsa-miR-221-5p | 2895 | 3916 | endothelial cells, immune cells | breast cancer,upregulated in thyroid cell transformation induced by HMGA1, TLR signal pathway in endotoxin tolerance , upregulated in T cell ALL | angiogenesis/vasculogenesis |
| hsa-miR-223-3p | 2898 | 3919 | meyloid cells | associated with CLL | |
| hsa-miR-223-5p | 2899 | 3920 | meyloid cells | associated with CLL | |

| | | | | | |
|---|---|---|---|---|---|
| hsa-miR-23b-3p | 2913 | 3934 | blood, myeloid cells | cancers (renal cancer, glioblastoma, prostate, etc) and autoimmune | |
| hsa-miR-23b-5p | 2914 | 3935 | blood, myeloid cells | cancers(glioblastoma, prostate, etc) and autoimmune | |
| hsa-miR-24-1-5p | 2916 | 3937 | lung, myeloid cells | | |
| hsa-miR-24-2-5p | 2917 | 3938 | lung, myeloid cells | | |
| hsa-miR-24-3p | 2918 | 3939 | lung, myeloid cells | | |
| hsa-miR-26a-1-3p | 2927 | 3948 | embryonic stem cells, blood (T cells) | chronic lymphocyte leukemia and other cancers | cell cycle and differentiation |
| hsa-miR-26a-2-3p | 2928 | 3949 | blood (Tcells), other tissues | chronic lymphocyte leukemia and other cancers | cell cycle and differentiation |
| hsa-miR-26a-5p | 2929 | 3950 | blood (Tcells), other tissues | chronic lymphocyte leukemia and other cancers | cell cycle and differentiation |
| hsa-miR-26b-3p | 2930 | 3951 | hematopoietic cells | | |
| hsa-miR-26b-5p | 2931 | 3952 | hematopoietic cells | | |
| hsa-miR-27a-3p | 2932 | 3953 | myeloid cells | various cancer cells | |
| hsa-miR-27a-5p | 2933 | 3954 | myeloid cells | various cancer cells | |
| hsa-miR-27b-3p | 2934 | 3955 | myeloid cells, vascular endothelial cells | various cancer cells | pro-angiogenic |
| hsa-miR-28-3p | 2936 | 3957 | blood(immune cells) | B/T cell lymphoma | |
| hsa-miR-28-5p | 2937 | 3958 | blood(immune cells) | B/T cell lymphoma | |
| hsa-miR-2909 | 2939 | 3960 | T-Lymphocytes | | |
| hsa-miR-29a-3p | 2948 | 3969 | immuno system, colonrectun | various cancers, neurodegenative disease | tumor suppression, immune modulation (mir-29 family) |
| hsa-miR-29a-5p | 2949 | 3970 | immuno system, colonrectun | various cancers, neurodegenative disease | adaptive immunity |
| hsa-miR-29b-1-5p | 2950 | 3971 | immuno system | associated with CLL, other cancers, neurodegenative disease | adaptive immunity |
| hsa-miR-29b-2-5p | 2951 | 3972 | immuno system | associated with CLL, other cancers, | adaptive immunity |
| hsa-miR-29b-3p | 2952 | 3973 | immuno system | associated with CLL, other cancers | adaptive immunity |
| hsa-miR-29c-3p | 2953 | 3974 | immuno system | associated with | adaptive |

| | | | | | |
|---|---|---|---|---|---|
| | | | | CLL, other cancers | immunity |
| hsa-miR-29c-5p | 2954 | 3975 | immuno system | associated with CLL, other cancers | adaptive immunity |
| hsa-miR-30e-3p | 2984 | 4005 | myeloid cells, glia cells | | |
| hsa-miR-30e-5p | 2985 | 4006 | myeloid cells, glia cells | | |
| hsa-miR-331-5p | 3130 | 4151 | lymphocytes | | |
| hsa-miR-339-3p | 3137 | 4158 | immune cells | | |
| hsa-miR-339-5p | 3138 | 4159 | immune cells | | |
| hsa-miR-345-3p | 3147 | 4168 | hematopoietic cells | increased in follicular lymphoma(53), other cancers | |
| hsa-miR-345-5p | 3148 | 4169 | hematopoietic cells | increased in follicular lymphoma(53) | |
| hsa-miR-346 | 3149 | 4170 | immume cells | cancers and autoimmune | |
| hsa-miR-34a-3p | 3150 | 4171 | breast, myeloid cells, ciliated epithelial cells | gastric cancer, CLL, other | tumor suppressor, p53 inducible |
| hsa-miR-34a-5p | 3151 | 4172 | breast, myeloid cells, ciliated epithelial cells | gastric cancer, CLL, other | tumor suppressor, p53 inducible |
| hsa-miR-363-3p | 3193 | 4214 | kidney stem cell, blood cells | | |
| hsa-miR-363-5p | 3194 | 4215 | kidney stem cell, blood cells | | |
| hsa-miR-372 | 3277 | 4298 | hematopoietic cells, lung, placental (blood) | | |
| hsa-miR-377-3p | 3294 | 4315 | hematopoietic cells | | |
| hsa-miR-377-5p | 3295 | 4316 | hematopoietic cells | | |
| hsa-miR-493-3p | 4947 | 5968 | myeloid cells, pancreas (islet) | | |
| hsa-miR-493-5p | 4948 | 5969 | myeloid cells, pancreas (islet) | | |
| hsa-miR-542-3p | 5106 | 6127 | monocytes | | targets to survivin , introduce growth arrest |
| hsa-miR-548b-5p | 5157 | 6178 | immune cells frontal cortex | | |
| hsa-miR-548c-5p | 5159 | 6180 | immune cells frontal cortex | | |
| hsa-miR-548i | 5168 | 6189 | embryonic stem cells (41), immune cells | | |
| hsa-miR-548j | 5169 | 6190 | immune cells | | |

| | | | | | |
|---|---|---|---|---|---|
| hsa-miR-548n | 5173 | 6194 | embryonic stem cells , immune cells | | |
| hsa-miR-574-3p | 5279 | 6300 | blood (myeloid cells) | increased in follicular lymphoma(53) | |
| hsa-miR-598 | 5310 | 6331 | in blood lymphocytes (PBL) | | |
| hsa-miR-935 | 5547 | 6568 | identified in human cervical cancer blood mononuclear cells | associated with energy metabolism/obesity, medullablastoma/neural stem cells | |
| hsa-miR-99a-3p | 5567 | 6588 | hemapoietic cells | | |
| hsa-miR-99a-5p | 5568 | 6589 | hemapoietic cells, plasma (exosome) | | |
| hsa-miR-99b-3p | 5569 | 6590 | hemapoietic cells, Embryonic stem cells, | | |
| hsa-miR-99b-5p | 5570 | 6591 | hemapoietic cells, Embryonic stem cells , plasma(exosome) | | |

## III. Modifications

**[00340]** Herein, in a signal-sensor polynucleotide (such as a primary construct or a mRNA molecule), the terms "modification" or, as appropriate, "modified" refer to modification with respect to A, G, U or C ribonucleotides. Generally, herein, these terms are not intended to refer to the ribonucleotide modifications in naturally occurring 5′-terminal mRNA cap moieties. In a polypeptide, the term "modification" refers to a modification as compared to the canonical set of 20 amino acids.

**[00341]** The modifications may be various distinct modifications. In some embodiments, the coding region, the flanking regions and/or the terminal regions may contain one, two, or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified signal-sensor polynucleotide, primary construct, or mmRNA introduced to a cell may exhibit reduced degradation in the cell, as compared to an unmodified signal-sensor polynucleotide, primary construct, or mmRNA.

**[00342]** The signal-sensor polynucleotides, primary constructs, and mmRNA can include any useful modification, such as to the sugar, the nucleobase, or the

internucleoside linkage (*e.g.* to a linking phosphate / to a phosphodiester linkage / to the phosphodiester backbone). One or more atoms of a pyrimidine nucleobase may be replaced or substituted with optionally substituted amino, optionally substituted thiol, optionally substituted alkyl (e.g., methyl or ethyl), or halo (e.g., chloro or fluoro). In certain embodiments, modifications (e.g., one or more modifications) are present in each of the sugar and the internucleoside linkage. Modifications according to the present invention may be modifications of ribonucleic acids (RNAs) to deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof). Additional modifications are described herein.

**[00343]** As described herein, in some embodiments, the signal-sensor polynucleotides, primary constructs, and mmRNA of the invention do not substantially induce an innate immune response of a cell into which the mRNA is introduced. Featues of an induced innate immune response include 1) increased expression of pro-inflammatory cytokines, 2) activation of intracellular PRRs (RIG-I, MDA5, etc, and/or 3) termination or reduction in protein translation. In other embodiments, an immune response is induced.

**[00344]** In certain embodiments, it may desirable to intracellularly degrade a modified nucleic acid molecule introduced into the cell. For example, degradation of a modified nucleic acid molecule may be preferable if precise timing of protein production is desired. Thus, in some embodiments, the invention provides a modified nucleic acid molecule containing a degradation domain, which is capable of being acted on in a directed manner within a cell.

**[00345]** In another aspect, the present disclosure provides signal-sensor polynucleotides comprising a nucleoside or nucleotide that can disrupt the binding of a major groove interacting, e.g. binding, partner with the polynucleotide (e.g., where the modified nucleotide has decreased binding affinity to major groove interacting partner, as compared to an unmodified nucleotide).

**[00346]** The signal-sensor polynucleotides, primary constructs, and mmRNA can optionally include other agents (e.g., RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc.). In some embodiments, the signal-sensor

polynucleotides, primary constructs, or mmRNA may include one or more messenger RNAs (mRNAs) and one or more modified nucleoside or nucleotides (e.g., mmRNA molecules). Details for these signal-sensor polynucleotides, primary constructs, and mmRNA follow.

*Signal-sensor Polynucleotides and Primary Constructs*

**[00347]** The signal-sensor polynucleotides, primary constructs, and mmRNA of the invention includes a first region of linked nucleosides encoding an oncology-related polypeptide of interest, a first flanking region located at the 5′ terminus of the first region, and a second flanking region located at the 3′ terminus of the first region.

**[00348]** In some embodiments, the signal-sensor polynucleotide, primary construct, or mmRNA are constructed according to the methods and modifications of International Application PCT/US12/058519 filed October 3, 2012 (M9), the contents of which are incorporated herein by reference in their entirety.

**[00349]** The signal-sensor polynucleotides, primary constructs, and mmRNA can optionally include 5′ and/or 3′ flanking regions, which are described herein.

*Signal-sensor Modified RNA (mmRNA) Molecules*

**[00350]** The present invention also includes the building blocks, e.g., modified ribonucleosides, modified ribonucleotides, of modified signal-sensor mRNA (mmRNA) molecules. For example, these building blocks can be useful for preparing the signal-sensor polynucleotides, primary constructs, or mmRNA of the invention. Such building blocks are taught in co-pending International Application PCT/US12/058519 filed October 3, 2012 (M9), the contents of which are incorporated herein by reference in their entirety.

*Modifications on the Nucleobase*

**[00351]** The present disclosure provides for modified nucleosides and nucleotides. As described herein “nucleoside” is defined as a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as “nucleobase”). As described herein, “nucleotide” is defined as a nucleoside including a phosphate group. In some embodiments, the nucleosides and nucleotides described

herein are generally chemically modified on the major groove face. Exemplary non-limiting modifications include an amino group, a thiol group, an alkyl group, a halo group, or any described herein. The modified nucleotides may by synthesized by any useful method, as described herein (e.g., chemically, enzymatically, or recombinantly to include one or more modified or non-natural nucleosides).

**[00352]** The modified nucleosides and nucleotides can include a modified nucleobase. Examples of nucleobases found in RNA include, but are not limited to, adenine, guanine, cytosine, and uracil. Examples of nucleobase found in DNA include, but are not limited to, adenine, guanine, cytosine, and thymine. These nucleobases can be modified or wholly replaced to provide signal-sensor polynucleotides, primary constructs, or mmRNA molecules having enhanced properties. For example, the nucleosides and nucleotides described herein can be chemically modified. In some embodiments, chemical modifications can include an amino group, a thiol group, an alkyl group, or a halo group.

*Modifications on the Internucleoside Linkage*

**[00353]** The modified nucleotides, which may be incorporated into a signal-sensor polynucleotide, primary construct, or mmRNA molecule, can be modified on the internucleoside linkage (e.g., phosphate backbone). Herein, in the context of the polynucleotide backbone, the phrases "phosphate" and "phosphodiester" are used interchangeably. Backbone phosphate groups can be modified by replacing one or more of the oxygen atoms with a different substituent. Further, the modified nucleosides and nucleotides can include the wholesale replacement of an unmodified phosphate moiety with another internucleoside linkage as described herein. Examples of modified phosphate groups include, but are not limited to, phosphorothioate, phosphoroselenates, boranophosphates, boranophosphate esters, hydrogen phosphonates, phosphoramidates, phosphorodiamidates, alkyl or aryl phosphonates, and phosphotriesters.

Phosphorodithioates have both non-linking oxygens replaced by sulfur. The phosphate linker can also be modified by the replacement of a linking oxygen with nitrogen (bridged phosphoramidates), sulfur (bridged phosphorothioates), and carbon (bridged methylene-phosphonates).

**[00354]** The α-thio substituted phosphate moiety is provided to confer stability to RNA and DNA polymers through the unnatural phosphorothioate backbone linkages. Phosphorothioate DNA and RNA have increased nuclease resistance and subsequently a longer half-life in a cellular environment. Phosphorothioate linked signal-sensor polynucleotides, primary constructs, or mmRNA molecules are expected to also reduce the innate immune response through weaker binding/activation of cellular innate immune molecules.

**[00355]** In specific embodiments, a modified nucleoside includes an alpha-thio-nucleoside (e.g., 5′-O-(1-thiophosphate)-adenosine, 5′-O-(1-thiophosphate)-cytidine (α-thio-cytidine), 5′-O-(1-thiophosphate)-guanosine, 5′-O-(1-thiophosphate)-uridine, or 5′-O-(1-thiophosphate)-pseudouridine).

**[00356]** Other internucleoside linkages that may be employed according to the present invention, including internucleoside linkages which do not contain a phosphorous atom, are described herein below.

*Combinations of Modified Sugars, Nucleobases, and Internucleoside Linkages*

**[00357]** The signal-sensor polynucleotides, primary constructs, and mmRNA of the invention can include a combination of modifications to the sugar, the nucleobase, and/or the internucleoside linkage. These combinations can include any one or more modifications described herein or in International Application PCT/US12/058519 filed October 3, 2012 (M9), the contents of which are incorporated herein by reference in their entirety.

*Synthesis of Signal-sensor primary constructs, and mmRNA Molecules*

**[00358]** The signal-sensor polypeptides, primary constructs, and mmRNA molecules for use in accordance with the invention may be prepared according to any useful technique, as described herein. The modified nucleosides and nucleotides used in the synthesis of signal-sensor polynucleotides, primary constructs, and mmRNA molecules disclosed herein can be prepared from readily available starting materials using the following general methods and procedures. Where typical or preferred process conditions (e.g., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are provided, a skilled artisan would be able to optimize and develop additional process conditions. Optimum reaction conditions may vary with the particular

reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

**[00359]** The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., $^{1}H$ or $^{13}C$) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

**[00360]** Preparation of signal-sensor polynucleotides, primary constructs, and mmRNA molecules of the present invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

**[00361]** The reactions of the processes described herein can be carried out in suitable solvents, which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

**[00362]** Resolution of racemic mixtures of modified nucleosides and nucleotides (e.g., mmRNA molecules) can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids. Resolution of racemic mixtures can also be carried out by elution on a column packed with an

optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

**[00363]** Modified nucleosides and nucleotides (e.g., building block molecules) can be prepared according to the synthetic methods described in Ogata et al., J. Org. Chem. 74:2585-2588 (2009); Purmal et al., Nucl. Acids Res. 22(1): 72-78, (1994); Fukuhara et al., Biochemistry, 1(4): 563-568 (1962); and Xu et al., Tetrahedron, 48(9): 1729-1740 (1992), each of which are incorporated by reference in their entirety.

**[00364]** The signal-sensor polynucleotides, primary constructs, and mmRNA of the invention may or may not be uniformly modified along the entire length of the molecule. For example, one or more or all types of nucleotide (*e.g.*, purine or pyrimidine, or any one or more or all of A, G, U, C) may or may not be uniformly modified in a polynucleotide of the invention, or in a given predetermined sequence region thereof (*e.g.* one or more of the sequence regions represented in Figure 1). In some embodiments, all nucleotides X in a signal-sensor polynucleotide of the invention (or in a given sequence region thereof) are modified, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C.

**[00365]** Different sugar modifications, nucleotide modifications, and/or internucleoside linkages (e.g., backbone structures) may exist at various positions in the signal-sensor polynucleotide, primary construct, or mmRNA. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a signal-sensor polynucleotide, primary construct, or mmRNA such that the function of the signal-sensor polynucleotide, primary construct, or mmRNA is not substantially decreased. A modification may also be a 5′ or 3′ terminal modification. The signal-sensor polynucleotide, primary construct, or mmRNA may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e. any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from

20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%).

**[00366]** In some embodiments, the signal-sensor polynucleotide, primary construct, or mmRNA includes a modified pyrimidine (e.g., a modified uracil/uridine/U or modified cytosine/cytidine/C). In some embodiments, the uracil or uridine (generally: U) in the signal-sensor polynucleotide, primary construct, or mmRNA molecule may be replaced with from about 1% to about 100% of a modified uracil or modified uridine (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100% of a modified uracil or modified uridine). The modified uracil or uridine can be replaced by a compound having a single unique structure or by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures, as described herein). In some embodiments, the cytosine or cytidine (generally: C) in the signal-sensor polynucleotide, primary construct, or mmRNA molecule may be replaced with from about 1% to about 100% of a modified cytosine or modified cytidine (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%,

from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100% of a modified cytosine or modified cytidine). The modified cytosine or cytidine can be replaced by a compound having a single unique structure or by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures, as described herein).

*Combinations of Nucleotides*

**[00367]** Further examples of modified nucleotides and modified nucleotide combinations are provided in International Application PCT/US12/058519 filed October 3, 2012 (M9) the contents of which are incorporated herein by reference in their entirety.

**[00368]** In some embodiments, at least 25% of the cytidines are replaced (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

**[00369]** In some embodiments, at least 25% of the uracils are replaced (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

**[00370]** In some embodiments, at least 25% of the cytidines are replaced, and at least 25% of the uracils are replaced (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

## IV. Pharmaceutical Compositions

*Formulation, Administration, Delivery and Dosing*

**[00371]** The present invention provides signal-sensor polynucleotides, primary constructs and mmRNA compositions and complexes in combination with one or more pharmaceutically acceptable excipients. Pharmaceutical compositions may optionally

comprise one or more additional active substances, e.g. therapeutically and/or prophylactically active substances. General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

**[00372]** In some embodiments, compositions are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to signal-sensor polynucleotides, primary constructs and mmRNA to be delivered as described herein.

**[00373]** Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, *e.g.,* to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

**[00374]** Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

**[00375]** A pharmaceutical composition in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical

composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

**[00376]** Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

*Formulations*

**[00377]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (e.g., from a depot formulation of the signal-sensor polynucleotide, primary construct, or mmRNA); (4) alter the biodistribution (e.g., target the polynucleotide, primary construct, or mmRNA to specific tissues or cell types); (5) increase the translation of encoded protein *in vivo*; and/or (6) alter the release profile of encoded protein in vivo. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients of the present invention can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with signal-sensor polynucleotide, primary construct, or mmRNA (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof. Further, the signal-sensor polynucleotide, primary construct, or mmRNA of the present invention may be formulated using self-assembled nucleic acid nanoparticles.

**[00378]** Accordingly, the formulations of the invention can include one or more excipients, each in an amount that together increases the stability of the signal-sensor polynucleotide, primary construct, or mmRNA, increases cell transfection by the signal-

sensor polynucleotide, primary construct, or mmRNA, increases the expression of polynucleotide, primary construct, or mmRNA encoded protein, and/or alters the release profile of signal-sensor polynucleotide, primary construct, or mmRNA encoded proteins. Further, the primary construct and mmRNA of the present invention may be formulated using self-assembled nucleic acid nanoparticles.

**[00379]** Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients.

**[00380]** A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient may generally be equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage including, but not limited to, one-half or one-third of such a dosage.

**[00381]** Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient.

**[00382]** In some embodiments, the formulations described herein may contain at least one signal-sensor mmRNA. As a non-limiting example, the formulations may contain 1, 2, 3, 4 or 5 signal-sensor mmRNA. In one embodiment the formulation may contain modified mRNA encoding proteins selected from categories such as, proteins. In one embodiment, the formulation contains at least three signal-sensor modified mRNA encoding oncology-related proteins. In one embodiment, the formulation contains at least five signal-sensor modified mRNA encoding oncology-related proteins.

**[00383]** Pharmaceutical formulations may additionally comprise a pharmaceutically acceptable excipient, which, as used herein, includes, but is not limited to, any and all

solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

**[00384]** In some embodiments, the particle size of the lipid nanoparticle may be increased and/or decreased. The change in particle size may be able to help counter biological reaction such as, but not limited to, inflammation or may increase the biological effect of the signal-sensor modified mRNA delivered to mammals.

**[00385]** Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, surface active agents and/or emulsifiers, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in the pharmaceutical formulations of the invention.

**[00386]** Pharmaceutical compositions of the present invention may comprise at least one adjuvant which may be a chemo-adjuvant. Non-limiting examples of chemo-adjuvants and delivery systems which comprises a chemo-adjuvant are described in International Patent Publication No. WO2013134349, the contents of which is herein incorporated by reference in its entirety. The chemo-adjuvant may be bonded to, non-covalently bonded to or encapsulated within a delivery vehicle described herein.

*Lipidoids*

**[00387]** The synthesis of lipidoids has been extensively described and formulations containing these compounds are particularly suited for delivery of signal-sensor polynucleotides, primary constructs or mmRNA (see Mahon et al., Bioconjug Chem. 2010 21:1448-1454; Schroeder et al., J Intern Med. 2010 267:9-21; Akinc et al., Nat

Biotechnol. 2008 26:561-569; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-3001; all of which are incorporated herein in their entireties).

**[00388]** While these lipidoids have been used to effectively deliver double stranded small interfering RNA molecules in rodents and non-human primates (see Akinc et al., Nat Biotechnol. 2008 26:561-569; Frank-Kamenetsky et al., Proc Natl Acad Sci U S A. 2008 105:11915-11920; Akinc et al., Mol Ther. 2009 17:872-879; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Leuschner et al., Nat Biotechnol. 2011 29:1005-1010; all of which is incorporated herein in their entirety), the present disclosure describes their formulation and use in delivering single stranded signal-sensor polynucleotides, primary constructs, or mmRNA. Complexes, micelles, liposomes or particles can be prepared containing these lipidoids and therefore, can result in an effective delivery of the signal-sensor polynucleotide, primary construct, or mmRNA, as judged by the production of an encoded protein, following the injection of a lipidoid formulation via localized and/or systemic routes of administration. Lipidoid complexes of signal-sensor polynucleotides, primary constructs, or mmRNA can be administered by various means including, but not limited to, intravenous, intramuscular, or subcutaneous routes.

**[00389]** *In vivo* delivery of nucleic acids may be affected by many parameters, including, but not limited to, the formulation composition, nature of particle PEGylation, degree of loading, oligonucleotide to lipid ratio, and biophysical parameters such as particle size (Akinc et al., Mol Ther. 2009 17:872-879; herein incorporated by reference in its entirety). As an example, small changes in the anchor chain length of poly(ethylene glycol) (PEG) lipids may result in significant effects on in vivo efficacy. Formulations with the different lipidoids, including, but not limited to penta[3-(1-laurylaminopropionyl)]-triethylenetetramine hydrochloride (TETA–5LAP; aka 98N12-5, see Murugaiah et al., Analytical Biochemistry, 401:61 (2010)), C12-200 (including derivatives and variants), and MD1, can be tested for *in vivo* activity.

**[00390]** The lipidoid referred to herein as "98N12-5" is disclosed by Akinc et al., Mol Ther. 2009 17:872-879 and is incorporated by reference in its entirety.

**[00391]** The lipidoid referred to herein as "C12-200" is disclosed by Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869 and Liu and Huang, Molecular Therapy. 2010 669-670; both of which are herein incorporated by reference in their entirety. The lipidoid formulations can include particles comprising either 3 or 4 or more components in addition to signal-sensor polynucleotide, primary construct, or mmRNA. As an example, formulations with certain lipidoids, include, but are not limited to, 98N12-5 and may contain 42% lipidoid, 48% cholesterol and 10% PEG (C14 alkyl chain length). As another example, formulations with certain lipidoids, include, but are not limited to, C12-200 and may contain 50% lipidoid, 10% disteroylphosphatidyl choline, 38.5% cholesterol, and 1.5% PEG-DMG.

**[00392]** Combinations of different lipidoids may be used to improve the efficacy of signal-sensor polynucleotide, primary construct, or mmRNA directed protein production as the lipidoids may be able to increase cell transfection by the signal-sensor polynucleotide, primary construct, or mmRNA; and/or increase the translation of encoded oncology-related protein (see Whitehead et al., Mol. Ther. 2011, 19:1688-1694, herein incorporated by reference in its entirety).

**[00393]** In some embodiments, the particle size of the lipid nanoparticle may be increased and/or decreased. The change in particle size may be able to help counter biological reaction such as, but not limited to, inflammation or may increase the biological effect of , the signal-sensor polynucleotide, primary construct, or mmRNA delivered to subjects.

*Liposomes, Lipoplexes, and Lipid Nanoparticles*

**[00394]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In one embodiment, pharmaceutical compositions of signal-sensor polynucleotide, primary construct, or mmRNA include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a

small unicellular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

**[00395]** The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients , the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

**[00396]** In one embodiment, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-*N,N*-dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, WA), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, PA).

**[00397]** In one embodiment, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge et al. J Clin Invest. 2009 119:661-673; deFougerolles *Hum Gene Ther.* 2008

19:125-132; all of which are incorporated herein in their entireties.) The original manufacture method by Wheeler et al. was a detergent dialysis method, which was later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the signal-sensor polynucleotide, primary construct, or mmRNA. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleyloxy-*N,N*-dimethylaminopropane (DODMA), as described by Jeffs et al. As another example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-*N,N*-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

**[00398]** In one embdodiment, pharmaceutical compsotions may include liposomes which may be formed to deliver signal-sensor mmRNA which may encode at least one immunogen. The mmRNA may be encapsulated by the liposome and/or it may be contained in an acqueous core which may then be encapsulated by the liposome (see International Pub. Nos. WO2012031046, WO2012031043, WO201203091 and WO2012006378 herein incorporated by reference in their entireties). In another embodiment, the signal-sensor mmRNA which may encode an immunogen may be formulated in a cationic oil-in-water emulstion where the emulsion particle comprises an oil core and a cationic lipid which can interact with the signal-sensor mmRNA anchoring the molecule to the emulsion particle (see International Pub. No. WO2012006380). In yet another embodiment, the lipid formulation may include at least cationic lipid, a lipid which may enhance transfection and a least one lipid which contains a hydrophilic head group linked to a lipid moiety (International Pub. No. WO2011076807 and U.S. Pub. No. 20110200582; herein incorporated by reference in their entireties). In another embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA encoding an immunogen may be formulated in a lipid vesicle which may have crosslinks between functionalized lipid bilayers (see U.S. Pub. No. 20120177724, herein incorporated by reference in its entirety).

**[00399]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid vesicle which may have crosslinks between functionalized lipid bilayers.

**[00400]** In one embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine. In another embodiment, the signal-sensor polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid-polycation complex which may further include a neutral lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

**[00401]** The liposome formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (Semple et al. Nature Biotech. 2010 28:172-176), the liposome formulation was composed of 57.1 % cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3 % cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid could more effectively deliver siRNA to various antigen presenting cells (Basha et al. Mol Ther. 2011 19:2186-2200; herein incorporated by reference in its entirety).

**[00402]** In some embodiments, the ratio of PEG in the LNP formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain 1-5% of the lipid molar ratio of PEG-c-DOMG as compared to the cationic lipid, DSPC and cholesterol. In another embodiment the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG- DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol) or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The

cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

**[00403]** In one embodiment, the LNP formulations of the signal-sensor polynucleotides, primary constructs and/or mmRNA may contain PEG-c-DOMG 3% lipid molar ratio. In another embodiment, the LNP formulations of the signal-sensor polynucleotides, primary constructs and/or mmRNA may contain PEG-c-DOMG 1.5% lipid molar ratio.

**[00404]** In one embodiment, the pharmaceutical compositions of the signal-sensor polynucleotides, primary constructs and/or mmRNA may include at least one of the PEGylated lipids described in International Publication No. 2012099755, herein incorporated by reference.

**[00405]** In one embodiment, the pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (e.g., siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713)) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

**[00406]** In some embodiments the liposome may be a liposomal nanostructure which has been formulated for treatment of cancers and other diseases or to control the cholesterol metabolism in cells. The liposome nanostructure may also comprise a scavenger receptor type B-1 (SR-B1) in order to kill cancer cells. Non-limiting examples of liposomal nanostructures, which may be used with the signal-sensor polynucleotides described herein, are described in International Publication No. WO2013126776, the contents of which are herein incorporated by reference in its entirety.

**[00407]** In one embodiment, the liposomes described herein may comprise at least one immunomodulator such as, but not limited to, cytokines. Formulations and methods of using the liposomes comprising at least one immunomodulator are described in International Publication No WO2013129935 and WO2013129936, the contents of each of which are herein incorporated by reference in their entirety. As a non-limiting example, the liposomes comprising at least one immunomodulator may be used in the treatment of cancer. The liposomes comprising an immunomodulator may comprise a

signal-sensor polynucleotide described herein. As a non-limiting example, the liposome comprising an immunomodulator may be used in a combination with at least one antibody such as the particulate or vesicular immunomodulators described in International Publication No WO2013129936, the contents of which are herein incorporated by reference in its entirety.

**[00408]** Lipid nanoparticle formulations may be improved by replacing the cationic lipid with a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

**[00409]** In one embodiment, the internal ester linkage may be located on either side of the saturated carbon.

**[00410]** In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; herein incorporated by reference in their entireties). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant oncology-related protein, a signal-sensor modified RNA and/or a primary construct described herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

**[00411]** Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limted to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine,

large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosla tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. Adv Drug Deliv Rev. 2009 61(2): 158-171; herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT).

**[00412]** The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers),

polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer, and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see US Publication 20120121718 and US Publication 20100003337; herein incorporated by reference in their entireties). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; herein incorporated by reference in its entirety).

**[00413]** The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

**[00414]** The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, signal-sensor mmRNA, anionic protein (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase.. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see US Publication 20100215580 and US Publication 20080166414; herein incorporated by reference in their entireties).

**[00415]** The mucus penetrating lipid nanoparticles may comprise at least one signal-sensor mmRNA described herein. The signal-sensor mmRNA may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the paricle. The signal-sensor mmRNA may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

**[00416]** Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limted to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is

continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosla tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. Adv Drug Deliv Rev. 2009 61(2): 158-171; herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT).

**[00417]** The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may including, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes,

derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer, and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see US Publication 20120121718 and US Publication 20100003337; herein incorporated by reference in their entireties).

**[00418]** The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

**[00419]** The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, mmRNA, anionic protein (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase.. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see US Publication 20100215580 and US Publication 20080166414; herein incorporated by reference in their entireties).

**[00420]** The mucus penetrating lipid nanoparticles may comprise at least one signal-sensor polynucleotide, primary construct, or mmRNA described herein. The signal-sensor polynucleotide, primary construct, or mmRNA may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the paricle. The signal-sensor polynucleotide, primary construct, or mmRNA may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the surrounding mucus to decrease mucoadhesion which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

**[00421]** In one embodiment, the nanoparticle may be for a dual modality therapy such as described by Mieszawska et al. (Bioconjugate Chemistry, 2013, 24 (9), pp 1429–1434; the contents of which is herein incorporated by reference in its entirety) comprising at least one therapeutic agent (e.g., a signal-sequence polynucleotide described herein). The therapeutic agent or agents formulated in the lipid nanoparticle may be an anti-angiogenic and a cytotoxic agent (see e.g., the polymer-lipid nanoparticles taught by Mieszawska et al. Bioconjugate Chemistry, 2013, 24 (9), pp 1429–1434; the contents of which is herein incorporated by reference in its entirety).

**[00422]** In another embodiment, the nanoparticle may comprise a LyP-1 peptide such as the nanocarrier composition described in International Patent Publication No. WO2013100869, the contents of which are herein incorporated by reference in its entirety. The LyP-1 peptide may be contained in the nanoparticles disclosed herein, or may be a conjugate, derivative, analogue or pegylated form of the peptide. In one embodiment, a nanoparticle comprising the LyP-1 peptide may comprise a signal-sensor polynucleotide and may be used for cancer treatment and/or imaging.

**[00423]** In one embodiment, the signal-sensor polynucleotide, primary construct, or mmRNA is formulated as a lipoplex, such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT™ from STEMGENT® (Cambridge, MA), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids acids (Aleku et al. Cancer Res. 2008 68:9788-9798;

Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci U S A. 2007 6;104:4095-4100; deFougerolles *Hum Gene Ther.* 2008 19:125-132; all of which are incorporated herein by reference in its entirety).

**[00424]** In one embodiment such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types *in vivo*, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and MC3-based lipid nanoparticle formulations which have been shown to bind to apolipoprotein E and promote binding and uptake of these formulations into hepatocytes in vivo (Akinc et al. Mol Ther. 2010 18:1357-1364; herein incorporated by reference in its entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, *Front Biosci.* 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-

507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety)..

**[00425]** In one embodiment, the signal-sensor polynucleotide, primary construct, or mmRNA is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In a further embodiment, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696–1702; herein incorporated by reference in its entirety).

**[00426]** Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of signal-sensor polynucleotide, primary construct, or mmRNA directed protein production as these formulations may be able to increase cell transfection by the signal-sensor polynucleotide, primary construct, or mmRNA; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15:713-720; herein incorporated by reference in its entirety). The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the signal-sensor polynucleotide, primary construct, or mmRNA.

*Polymers, Biodegradable Nanoparticles, and Core-Shell Nanoparticles*

**[00427]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can be formulated using natural and/or synthetic polymers. Non-limiting examples of polymers which may be used for delivery include, but are not limited to, Dynamic POLYCONJUGATE™ formulations from MIRUS® Bio (Madison, WI) and Roche Madison (Madison, WI), PHASERX™ polymer formulations such as, without limitation, SMARTT POLYMER TECHNOLOGY™ (Seattle, WA), DMRI/DOPE, poloxamer, VAXFECTIN® adjuvant from Vical (San Diego, CA), chitosan, cyclodextrin from Calando Pharmaceuticals (Pasadena, CA), dendrimers and poly(lactic-co-glycolic acid) (PLGA) polymers. RONDEL™ (RNAi/Oligonucleotide Nanoparticle Delivery)

polymers (Arrowhead Research Corporation, Pasadena, CA) and pH responsive co-block polymers such as, but not limited to, PHASERX$^{TM}$ (Seattle, WA).

**[00428]** A non-limiting example of PLGA formulations include, but are not limited to, PLGA injectable depots (e.g., ELIGARD® which is formed by dissolving PLGA in 66% N-methyl-2-pyrrolidone (NMP) and the remainder being aqueous solvent and leuprolide. Once injected, the PLGA and leuprolide peptide precipitates into the subcutaneous space).

**[00429]** Many of these polymer approaches have demonstrated efficacy in delivering oligonucleotides *in vivo* into the cell cytoplasm (reviewed in deFougerolles *Hum Gene Ther.* 2008 19:125-132; herein incorporated by reference in its entirety). Two polymer approaches that have yielded robust *in vivo* delivery of nucleic acids, in this case with small interfering RNA (siRNA), are dynamic polyconjugates and cyclodextrin-based nanoparticles. The first of these delivery approaches uses dynamic polyconjugates and has been shown *in vivo* in mice to effectively deliver siRNA and silence endogenous target mRNA in hepatocytes (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887). This particular approach is a multicomponent polymer system whose key features include a membrane-active polymer to which nucleic acid, in this case siRNA, is covalently coupled via a disulfide bond and where both PEG (for charge masking) and *N*-acetylgalactosamine (for hepatocyte targeting) groups are linked via pH-sensitive bonds (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887). On binding to the hepatocyte and entry into the endosome, the polymer complex disassembles in the low-pH environment, with the polymer exposing its positive charge, leading to endosomal escape and cytoplasmic release of the siRNA from the polymer. Through replacement of the *N*-acetylgalactosamine group with a mannose group, it was shown one could alter targeting from asialoglycoprotein receptor-expressing hepatocytes to sinusoidal endothelium and Kupffer cells. Another polymer approach involves using transferrin-targeted cyclodextrin-containing polycation nanoparticles. These nanoparticles have demonstrated targeted silencing of the *EWS-FLI1* gene product in transferrin receptor-expressing Ewing's sarcoma tumor cells (Hu-Lieskovan *et al*., Cancer Res.2005 65: 8984-8982) and siRNA formulated in these nanoparticles was well tolerated in non-human primates (Heidel *et al*., Proc Natl Acad Sci USA 2007 104:5715-21). Both of

these delivery strategies incorporate rational approaches using both targeted delivery and endosomal escape mechanisms.

**[00430]** The polymer formulation can permit the sustained or delayed release of signal-sensor polynucleotide, primary construct, or mmRNA (e.g., following intramuscular or subcutaneous injection). The altered release profile for the signal-sensor polynucleotide, primary construct, or mmRNA can result in, for example, translation of an encoded protein over an extended period of time. The polymer formulation may also be used to increase the stability of the signal-sensor polynucleotide, primary construct, or mmRNA. Biodegradable polymers have been previously used to protect nucleic acids other than mmRNA from degradation and been shown to result in sustained release of payloads in vivo (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Sullivan et al., Expert Opin Drug Deliv. 2010 7:1433-1446; Convertine et al., Biomacromolecules. 2010 Oct 1; Chu et al., Acc Chem Res. 2012 Jan 13; Manganiello et al., Biomaterials. 2012 33:2301-2309; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Singha et al., Nucleic Acid Ther. 2011 2:133-147; deFougerolles Hum Gene Ther. 2008 19:125-132; Schaffert and Wagner, Gene Ther. 2008 16:1131-1138; Chaturvedi et al., Expert Opin Drug Deliv. 2011 8:1455-1468; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; herein incorporated by reference in its entirety).

**[00431]** In one embodiment, the pharmaceutical compositions may be sustained release formulations. In a further embodiment, the sustained release formulations may be for subcutaneous delivery. Sustained release formulations may include, but are not limited to, PLGA microspheres, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA). TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, IL).

**[00432]** As a non-limiting example modified mRNA may be formulated in PLGA microspheres by preparing the PLGA microspheres with tunable release rates (e.g., days and weeks) and encapsulating the signal-sensor modified mRNA in the PLGA microspheres while maintaining the integrity of the signal-sensor modified mRNA during the encapsulation process. EVAc are non-biodegradeable, biocompatible polymers

which are used extensively in pre-clinical sustained release implant applications (e.g., extended release products Ocusert a pilocarpine ophthalmic insert for glaucoma or progestasert a sustained release progesterone intrauterine deivce; transdermal delivery systems Testoderm, Duragesic and Selegiline; catheters). Poloxamer F-407 NF is a hydrophilic, non-ionic surfactant triblock copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene having a low viscosity at temperatures less than 5°C and forms a solid gel at temperatures greater than 15°C. PEG-based surgical sealants comprise two synthetic PEG components mixed in a delivery device which can be prepared in one minute, seals in 3 minutes and is reabsorbed within 30 days. GELSITE® and natural polymers are capable of in-situ gelation at the site of administration. They have been shown to interact with protein and peptide therapeutic candidates through ionic ineraction to provide a stabilizing effect.

**[00433]** Polymer formulations can also be selectively targeted through expression of different ligands as exemplified by, but not limited by, folate, transferrin, and N-acetylgalactosamine (GalNAc) (Benoit et al., Biomacromolecules. 2011 12:2708-2714; Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; herein incorporated by reference in its entirety).

**[00434]** The signal-sensor mmRNA of the invention may be formulated with or in a polymeric compound. The polymer may include at least one polymer such as, but not limited to, polyethylene glycol (PEG), poly(l-lysine)(PLL), PEG grafted to PLL, cationic lipopolymer, biodegradable cationic lipopolymer, polyethyleneimine (PEI), cross-linked branched poly(alkylene imines), a polyamine derivative, a modified poloxamer, a biodegradable polymer, biodegradable block copolymer, biodegradable random copolymer, biodegradable polyester copolymer, biodegradable polyester block copolymer, biodegradable polyester block random copolymer, linear biodegradable copolymer, poly[α-(4-aminobutyl)-L-glycolic acid) (PAGA), biodegradable cross-linked cationic multi-block copolymers or combinations thereof .

**[00435]** As a non-limiting example, the signal-sensor mmRNA of the invention may be formulated with the polymeric compound of PEG grafted with PLL as described in U.S. Pat. No. 6,177,274 herein incorporated by reference in its entirety. The formulation may

be used for transfecting cells *in vitro* or for *in vivo* delivery of the signal-sensor mmRNA. In another example, the signal-sensor mmRNA may be suspended in a solution or medium with a cationic polymer, in a dry pharmaceutical composition or in a solution that is capable of being dried as described in U.S. Pub. Nos. 20090042829 and 20090042825 each of which are herein incorporated by reference in their entireties.

**[00436]** A polyamine derivative may be used to deliver nucleic acids or to treat and/or prevent a disease or to be included in an implantable or injectable device (U.S. Pub. No. 20100260817 herein incorporated by reference in its entirety). As a non-limiting example, a pharmaceutical composition may include the signal-sensor mmRNA and the polyamine derivative described in U.S. Pub. No. 20100260817 (the contents of which are incorporated herein by reference in its entirety.

**[00437]** For example, the signal-sensor mmRNA of the invention may be formulated in a pharmaceutical compound including a poly(alkylene imine), a biodegradable cationic lipopolymer, a biodegradable block copolymer, a biodegradable polymer, or a biodegradable random copolymer, a biodegradable polyester block copolymer, a biodegradable polyester polymer, a biodegradable polyester random copolymer, a linear biodegradable copolymer, PAGA, a biodegradable cross-linked cationic multi-block copolymer or combinations thereof. The biodegradable cationic lipopolymer may be made my methods known in the art and/or described in U.S. Pat. No. 6,696,038, U.S. App. Nos. 20030073619 and 20040142474 which is herein incorporated by reference in their entireties.The poly(alkylene imine) may be made using methods known in the art and/or as described in U.S. Pub. No. 20100004315, herein incorporated by reference in its entirety. The biodegradabale polymer, biodegradable block copolymer, the biodegradable random copolymer, biodegradable polyester block copolymer, biodegradable polyester polymer, or biodegradable polyester random copolymer may be made using methods known in the art and/or as described in U.S. Pat. Nos. 6,517,869 and 6,267,987, the contents of which are each incorporated herein by reference in its entirety. The linear biodegradable copolymer may be made using methods known in the art and/or as described in U.S. Pat. No. 6,652,886. The PAGA polymer may be made using methods known in the art and/or as described in U.S. Pat. Nos. 6,217,912 herein incorporated by reference in its entirety. The PAGA polymer may be copolymerized to

form a copolymer or block copolymer with polymers such as but not limited to, poly-L-lysine, polyargine, polyornithine, histones, avidin, protamines, polylactides and poly(lactide-co-glycolides). The biodegradable cross-linked cationic multi-block copolymers may be made my methods known in the art and/or as described in U.S. Pat. No. 8,057,821 or U.S. Pub. No. 2012009145 herein incorporated by reference in their entireties. For example, the multi-block copolymers may be synthesized using linear polyethyleneimine (LPEI) blocks which have distinct patterns as compared to branched polyethyleneimines. Further, the composition or pharmaceutical composition may be made by the methods known in the art, described herein, or as described in U.S. Pub. No. 20100004315 or U.S. Pat. Nos. 6,267,987 and 6,217,912 herein incorporated by reference in their entireties.

**[00438]** As described in U.S. Pub. No. 20100004313, herein incorporated by reference in its entirety, a gene delivery composition may include a nucleotide sequence and a poloxamer. For example, the signal-sensor mmRNA of the present inveition may be used in a gene delivery composition with the poloxamer described in U.S. Pub. No. 20100004313.

**[00439]** In one embodiment, the polymer formulation of the present invention may be stabilized by contacting the polymer formulation, which may include a cationic carrier, with a cationic lipopolymer which may be covalently linked to cholesterol and polyethylene glycol groups. The polymer formulation may be contacted with a cationic lipopolymer using the methods described in U.S. Pub. No. 20090042829 herein incorporated by reference in its entirety. The cationic carrier may include, but is not limited to, polyethylenimine, poly(trimethylenimine), poly(tetramethylenimine), polypropylenimine, aminoglycoside-polyamine, dideoxy-diamino-b-cyclodextrin, spermine, spermidine, poly(2-dimethylamino)ethyl methacrylate, poly(lysine), poly(histidine), poly(arginine), cationized gelatin, dendrimers, chitosan, 1,2-Dioleoyl-3-Trimethylammonium-Propane(DOTAP), N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), 1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride (DOTIM), 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 3B-[N—(N′,N′-Dimethylaminoethane)-carbamoyl]Cholesterol Hydrochloride

(DC-Cholesterol HCl) diheptadecylamidoglycyl spermidine (DOGS), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), N,N-dioleyl-N,N-dimethylammonium chloride DODAC) and combinations thereof.

**[00440]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can also be formulated as a nanoparticle using a combination of polymers, lipids, and/or other biodegradable agents, such as, but not limited to, calcium phosphate. Components may be combined in a core-shell, hybrid, and/or layer-by-layer architecture, to allow for fine-tuning of the nanoparticle so to delivery of the signal-sensor polynucleotide, primary construct and mmRNA may be enhanced (Wang et al., Nat Mater. 2006 5:791-796; Fuller et al., Biomaterials. 2008 29:1526-1532; DeKoker et al., Adv Drug Deliv Rev. 2011 63:748-761; Endres et al., Biomaterials. 2011 32:7721-7731; Su et al., Mol Pharm. 2011 Jun 6;8(3):774-87; herein incorporated by reference in its entirety).

**[00441]** Biodegradable calcium phosphate nanoparticles in combination with lipids and/or polymers have been shown to deliver signal-sensor polynucleotides, primary constructs and mmRNA *in vivo*. In one embodiment, a lipid coated calcium phosphate nanoparticle, which may also contain a targeting ligand such as anisamide, may be used to deliver the signal-sensor polynucleotide, primary construct and mmRNA of the present invention. For example, to effectively deliver siRNA in a mouse metastatic lung model a lipid coated calcium phosphate nanoparticle was used (Li et al., J Contr Rel. 2010 142: 416-421; Li et al., J Contr Rel. 2012 158:108-114; Yang et al., Mol Ther. 2012 20:609-615). This delivery system combines both a targeted nanoparticle and a component to enhance the endosomal escape, calcium phosphate, in order to improve delivery of the siRNA.

**[00442]** In one embodiment, calcium phosphate with a PEG-polyanion block copolymer may be used to deliver signal-sensor polynucleotides, primary constructs and mmRNA (Kazikawa et al., J Contr Rel. 2004 97:345-356; Kazikawa et al., J Contr Rel. 2006 111:368-370).

**[00443]** In one embodiment, a PEG-charge-conversional polymer (Pitella et al., Biomaterials. 2011 32:3106-3114) may be used to form a nanoparticle to deliver the

signal-sensor polynucleotides, primary constructs and mmRNA of the present invention. The PEG-charge-conversional polymer may improve upon the PEG-polyanion block copolymers by being cleaved into a polycation at acidic pH, thus enhancing endosomal escape.

**[00444]** The use of core-shell nanoparticles has additionally focused on a high-throughput approach to synthesize cationic cross-linked nanogel cores and various shells (Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-13001). The complexation, delivery, and internalization of the polymeric nanoparticles can be precisely controlled by altering the chemical composition in both the core and shell components of the nanoparticle. For example, the core-shell nanoparticles may efficiently deliver siRNA to mouse hepatocytes after they covalently attach cholesterol to the nanoparticle.

**[00445]** In one embodiment, a hollow lipid core comprising a middle PLGA layer and an outer neutral lipid layer containg PEG may be used to delivery of the signal-sensor polynucleotide, primary construct and mmRNA of the present invention. As a non-limiting example, in mice bearing a luciferease-expressing tumor, it was determined that the lipid-polymer-lipid hybrid nanoparticle significantly suppressed luciferase expression, as compared to a conventional lipoplex (Shi et al, Angew Chem Int Ed. 2011 50:7027-7031).

*Peptides and Proteins*

**[00446]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can be formulated with peptides and/or proteins in order to increase transfection of cells by the polynucleotide, primary construct, or mmRNA. In one embodiment, peptides such as, but not limited to, cell penetrating peptides and proteins and peptides that enable intracellular delivery may be used to deliver pharmaceutical formulations. A non-limiting example of a cell penetrating peptide which may be used with the pharmaceutical formulations of the present invention includes a cell-penetrating peptide sequence attached to polycations that facilitates delivery to the intracellular space, e.g., HIV-derived TAT peptide, penetratins, transportans, or hCT derived cell-penetrating peptides (see, e.g., Caron et al., Mol. Ther. 3(3):310-8 (2001); Langel, Cell-Penetrating Peptides: Processes and Applications (CRC Press, Boca Raton FL, 2002); El-Andaloussi et al., Curr. Pharm. Des. 11(28):3597-611 (2003); and Deshayes et al.,

Cell. Mol. Life Sci. 62(16):1839-49 (2005), all of which are incorporated herein by reference). The compositions can also be formulated to include a cell penetrating agent, e.g., liposomes, which enhance delivery of the compositions to the intracellular space. signal-sensor polynucleotides, primary constructs, and mmRNA of the invention may be complexed to peptides and/or proteins such as, but not limited to, peptides and/or proteins from Aileron Therapeutics (Cambridge, MA) and Permeon Biologics (Cambridge, MA) in order to enable intracellular delivery (Cronican et al., ACS Chem. Biol. 2010 5:747-752; McNaughton et al., Proc. Natl. Acad. Sci. USA 2009 106:6111-6116; Sawyer, Chem Biol Drug Des. 2009 73:3-6; Verdine and Hilinski, Methods Enzymol. 2012;503:3-33; all of which are herein incorporated by reference in its entirety).

**[00447]** In one embodiment, the cell-penetrating polypeptide may comprise a first domain and a second domain. The first domain may comprise a supercharged polypeptide. The second domain may comprise a protein-binding partner. As used herein, "protein-binding partner" includes, but are not limited to, antibodies and functional fragments thereof, scaffold proteins, or peptides. The cell-penetrating polypeptide may further comprise an intracellular binding partner for the protein-binding partner. The cell-penetrating polypeptide may be capable of being secreted from a cell where the signal-sensor polynucleotide, primary construct, or mmRNA may be introduced.

**[00448]** Formulations of the including peptides or proteins may be used to increase cell transfection by the signal-sensor polynucleotide, primary construct, or mmRNA, alter the biodistribution of the signal-sensor polynucleotide, primary construct, or mmRNA (e.g., by targeting specific tissues or cell types), and/or increase the translation of encoded protein.

*Cells*

**[00449]** The signal-sensor polynucleotide, primary construct, and mmRNA of the invention can be transfected *ex vivo* into cells, which are subsequently transplanted into a subject. As non-limiting examples, the pharmaceutical compositions may include red blood cells to deliver modified RNA to liver and myeloid cells, virosomes to deliver modified RNA in virus-like particles (VLPs), and electroporated cells such as, but not limited to, from MAXCYTE® (Gaithersburg, MD) and from ERYTECH® (Lyon, France) to deliver modified RNA. Examples of use of red blood cells, viral particles and

electroporated cells to deliver payloads other than mmRNA have been documented (Godfrin et al., Expert Opin Biol Ther. 2012 12:127-133; Fang et al., Expert Opin Biol Ther. 2012 12:385-389; Hu et al., Proc Natl Acad Sci U S A. 2011 108:10980-10985; Lund et al., Pharm Res. 2010 27:400-420; Huckriede et al., J Liposome Res. 2007;17:39-47; Cusi, Hum Vaccin. 2006 2:1-7; de Jonge et al., Gene Ther. 2006 13:400-411; all of which are herein incorporated by reference in its entirety).

**[00450]** Cell-based formulations of the signal-sensor polynucleotide, primary construct, and mmRNA of the invention may be used to ensure cell transfection (e.g., in the cellular carrier), alter the biodistribution of the signal-sensor polynucleotide, primary construct, or mmRNA (e.g., by targeting the cell carrier to specific tissues or cell types), and/or increase the translation of encoded oncology-related protein.

**[00451]** A variety of methods are known in the art and suitable for introduction of nucleic acid into a cell, including viral and non-viral mediated techniques. Examples of typical non-viral mediated techniques include, but are not limited to, electroporation, calcium phosphate mediated transfer, nucleofection, sonoporation, heat shock, magnetofection, liposome mediated transfer, microinjection, microprojectile mediated transfer (nanoparticles), cationic polymer mediated transfer (DEAE-dextran, polyethylenimine, polyethylene glycol (PEG) and the like) or cell fusion.

**[00452]** The technique of sonoporation, or cellular sonication, is the use of sound (e.g., ultrasonic frequencies) for modifying the permeability of the cell plasma membrane. Sonoporation methods are known to those in the art and are used to deliver nucleic acids *in vivo* (Yoon and Park, Expert Opin Drug Deliv. 2010 7:321-330; Postema and Gilja, Curr Pharm Biotechnol. 2007 8:355-361; Newman and Bettinger, Gene Ther. 2007 14:465-475; all herein incorporated by reference in their entirety). Sonoporation methods are known in the art and are also taught for example as it relates to bacteria in US Patent Publication 20100196983 and as it relates to other cell types in, for example, US Patent Publication 20100009424, each of which are incorporated herein by reference in their entirety.

**[00453]** Electroporation techniques are also well known in the art and are used to deliver nucleic acids *in vivo* and clinically (Andre et al., Curr Gene Ther. 2010 10:267-280; Chiarella et al., Curr Gene Ther. 2010 10:281-286; Hojman, Curr Gene Ther. 2010

10:128-138; all herein incorporated by reference in their entirety). In one embodiment, signal-sensor polynucleotides, primary constructs or mmRNA may be delivered by electroporation as described in Example 12.

*Hyaluronidase*

**[00454]** The intramuscular or subcutaneous localized injection of signal-sensor polynucleotide, primary construct, or mmRNA of the invention can include hyaluronidase, which catalyzes the hydrolysis of hyaluronan. By catalyzing the hydrolysis of hyaluronan, a constituent of the interstitial barrier, hyaluronidase lowers the viscosity of hyaluronan, thereby increasing tissue permeability (Frost, Expert Opin. Drug Deliv. (2007) 4:427-440; herein incorporated by reference in its entirety). It is useful to speed their dispersion and systemic distribution of encoded proteins produced by transfected cells. Alternatively, the hyaluronidase can be used to increase the number of cells exposed to a signal-sensor polynucleotide, primary construct, or mmRNA of the invention administered intramuscularly or subcutaneously.

*Nanoparticle Mimics*

**[00455]** The signal-sensor polynucleotide, primary construct or mmRNA of the invention may be encapsulated within and/or absorbed to a nanoparticle mimic. A nanoparticle mimic can mimic the delivery function organisms or particles such as, but not limited to, pathogens, viruses, bacteria, fungus, parasites, prions and cells. As a non-limiting example the signal-sensor polynucleotide, primary construct or mmRNA of the invention may be encapsulated in a non-viron particle which can mimic the delivery function of a virus (see International Pub. No. WO2012006376 herein incorporated by reference in its entirety).

*Nanotubes*

**[00456]** The signal-sensor polynucleotides, primary constructs or mmRNA of the invention can be attached or otherwise bound to at least one nanotube such as, but not limited to, rosette nanotubes, rosette nanotubes having twin bases with a linker, carbon nanotubes and/or single-walled carbon nanotubes, The signal-sensor polynucleotides, primary constructs or mmRNA may be bound to the nanotubes through forces such as, but not limited to, steric, ionic, covalent and/or other forces.

**[00457]** In one embodiment, the nanotube can release one or more signal-sensor polynucleotides, primary constructs or mmRNA into cells. The size and/or the surface structure of at least one nanotube may be altered so as to govern the interaction of the nanotubes within the body and/or to attach or bind to the signal-sensor polynucleotides, primary constructs or mmRNA disclosed herein. In one embodiment, the building block and/or the functional groups attached to the building block of the at least one nanotube may be altered to adjust the dimensions and/or properties of the nanotube. As a non-limiting example, the length of the nanotubes may be altered to hinder the nanotubes from passing through the holes in the walls of normal blood vessels but still small enough to pass through the larger holes in the blood vessels of tumor tissue.

**[00458]** In one embodiment, at least one nanotube may also be coated with delivery enhancing compounds including polymers, such as, but not limited to, polyethylene glycol. In another embodiment, at least one nanotube and/or the signal-sensor polynucleotides, primary constructs or mmRNA may be mixed with pharmaceutically acceptable excipients and/or delivery vehicles.

**[00459]** In one embodiment, the signal-sensor polynucleotides, primary constructs or mmRNA are attached and/or otherwise bound to at least one rosette nanotube. The rosette nanotubes may be formed by a process known in the art and/or by the process described in International Publication No. WO2012094304, herein incorporated by reference in its entirety. At least one signal-sensor polynucleotide, primary construct and/or mmRNA may be attached and/or otherwise bound to at least one rosette nanotube by a process as described in International Publication No. WO2012094304, herein incorporated by reference in its entirety, where rosette nanotubes or modules forming rosette nanotubes are mixed in aqueous media with at least one signal-sensor polynucleotide, primary construct and/or mmRNA under conditions which may cause at least one signal-sensor polynucleotide, primary construct or mmRNA to attach or otherwise bind to the rosette nanotubes.

*Conjugates*

**[00460]** The signal-sensor polynucleotides, primary constructs, and mmRNA of the invention include conjugates, such as a polynucleotide, primary construct, or mmRNA covalently linked to a carrier or targeting group, or including two encoding regions that

together produce a fusion protein (e.g., bearing a targeting group and therapeutic protein or peptide).

**[00461]** The conjugates of the invention include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or globulin); an carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid, an oligonucleotide (e.g. an aptamer). Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

**[00462]** Representative U.S. patents that teach the preparation of polynucleotide conjugates, particularly to RNA, include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; each of which is herein incorporated by reference in their entirety.

**[00463]** In one embodiment, the conjugate of the present invention may function as a carrier for the signal-sensor mmRNA of the present invention. The conjugate may comprise a cationic polymer such as, but not limited to, polyamine, polylysine,

polyalkylenimine, and polyethylenimine which may be grafted to with poly(ethylene glycol). As a non-limiting example, the conjugate may be similar to the polymeric conjugate and the method of synthesizing the polymeric conjugate described in U.S. Pat. No. 6,586,524 herein incorporated by reference in its entirety.

**[00464]** The conjugates can also include targeting groups, e.g., a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, an RGD peptide, an RGD peptide mimetic or an aptamer.

**[00465]** Targeting groups can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Targeting groups may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, or aptamers. The ligand can be, for example, a lipopolysaccharide, or an activator of p38 MAP kinase.

**[00466]** The targeting group can be any ligand that is capable of targeting a specific receptor. Examples include, without limitation, folate, GalNAc, galactose, mannose, mannose-6P, apatamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL, and HDL ligands. In particular embodiments, the targeting group is an aptamer. The aptamer can be unmodified or have any combination of modifications disclosed herein.

**[00467]** In one embodiment, pharmaceutical compositions of the present invention may include chemical modifications such as, but not limited to, modifications similar to locked nucleic acids.

**[00468]** Representative U.S. Patents that teach the preparation of locked nucleic acid (LNA) such as those from Santaris, include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; and 7,399,845, each of which is herein incorporated by reference in its entirety.

**[00469]** Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

**[00470]** Some embodiments featured in the invention include signal-sensor polynucleotides, primary constructs or mmRNA with phosphorothioate backbones and oligonucleosides with other modified backbones, and in particular --$CH_2$--NH--$CH_2$--, --$CH_2$--$N(CH_3)$--O--$CH_2$--[known as a methylene (methylimino) or MMI backbone], --$CH_2$--O--$N(CH_3)$--$CH_2$--, --$CH_2$--$N(CH_3)$--$N(CH_3)$--$CH_2$-- and --$N(CH_3)$--$CH_2$--$CH_2$--[wherein the native phosphodiester backbone is represented as --O—$P(O)_2$--O--$CH_2$--] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the polynucletotides featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

**[00471]** Modifications at the 2′ position may also aid in delivery. Preferably, modifications at the 2′ position are not located in a polypeptide-coding sequence, i.e., not in a translatable region. Modifications at the 2′ position may be located in a 5′UTR, a 3′UTR and/or a tailing region. Modifications at the 2′ position can include one of the following at the 2' position: H (i.e., 2′-deoxy); F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted $C_1$ to $C_{10}$ alkyl or $C_2$ to $C_{10}$ alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)._nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, the signal-sensor polynucleotides, primary constructs or mmRNA include one of the following at the 2' position: $C_1$ to $C_{10}$ lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, $SCH_3$, OCN, Cl, Br, CN, $CF_3$, $OCF_3$, $SOCH_3$, $SO_2CH_3$, $ONO_2$, $NO_2$, $N_3$, $NH_2$, heterocycloalkyl, heterocycloalkaryl,

aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties, or a group for improving the pharmacodynamic properties, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--$CH_2$--O--$CH_2$--$N(CH_2)_2$, also described in examples herein below. Other modifications include 2'-methoxy (2'-$OCH_3$), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. signal-sensor polynucleotides of the invention may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920 and each of which is herein incorporated by reference.

**[00472]** In still other embodiments, the signal-sensor polynucleotide, primary construct, or mmRNA is covalently conjugated to a cell penetrating polypeptide. The cell-penetrating peptide may also include a signal peptide sequence. The conjugates of the invention can be designed to have increased stability; increased cell transfection; and/or altered the biodistribution (e.g., targeted to specific tissues or cell types).

*Self-Assembled Nucleic Acid Nanoparticles*

**[00473]** Self-assembled nanoparticles have a well-defined size which may be precisely controlled as the nucleic acid strands may be easily reprogrammable. For example, the optimal particle size for a cancer-targeting nanodelivery carrier is 20-100 nm as a diameter greater than 20 nm avoids renal clearance and enhances delivery to certain

tumors through enhanced permeability and retention effect. Using self-assembled nucleic acid nanoparticles a single uniform population in size and shape having a precisely controlled spatial orientation and density of cancer-targeting ligands for enhanced delivery. As a non-limiting example, oligonucleotide nanoparticles were prepared using programmable self-assembly of short DNA fragments and therapeutic siRNAs. These nanoparticles are molecularly identical with controllable particle size and target ligand location and density. The DNA fragments and siRNAs self-assembled into a one-step reaction to generate DNA/siRNA tetrahedral nanoparticles for targeted *in vivo* delivery. (Lee et al., Nature Nanotechnology 2012 7:389-393).

*Excipients*

**[00474]** Pharmaceutical formulations may additionally comprise a pharmaceutically acceptable excipient, which, as used herein, includes any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's *The Science and Practice of Pharmacy*, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

**[00475]** In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use in humans and for veterinary use. In some embodiments, an excipient is approved by United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

**[00476]** Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical compositions.

**[00477]** Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

**[00478]** Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and/or combinations thereof.

**[00479]** Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and VEEGUM® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty

acid esters (e.g. polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEENn®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [Span®60], sorbitan tristearate [Span®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLUORINC®F 68, POLOXAMER®188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

**[00480]** Exemplary binding agents include, but are not limited to, starch (*e.g.* cornstarch and starch paste); gelatin; sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol,); natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; *etc.*; and combinations thereof.

**[00481]** Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium

# DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 312

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# JUMBO APPLICATIONS/PATENTS

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NOTE POUR LE TOME / VOLUME NOTE:

# Claims

We claim:

1. An isolated synthetic signal-sensor polynucleotide, wherein said isolated synthetic signal-sensor polynucleotide comprises an mRNA which encodes an oncology-related polypeptide of interest and one or more sensor sequences selected from the group consisting of any of SEQ ID NOs: 3529-4549, SEQ ID NOs: 5571-6591 and functional variants thereof.

2. The isolated synthetic signal-sensor polynucleotide of claim 1 wherein the oncology-related polypeptide of interest is selected from the group consisting of SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516 and 7517.

3. The isolated synthetic signal-sensor polynucleotide of claim 1 wherein the mRNA comprises at least an open reading frame of a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 2488-2496, 6617-6621, 7348-7354, 7362-7489, 7491, 7494, 7506, 7511 and 7513.

4. The isolated synthetic signal-sensor polynucleotide of claim 3, wherein the open reading frame is codon optimized.

5. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the mRNA comprises two stop codons.

6. The isolated synthetic signal-sensor isolated polynucleotide of claim 1, wherein the mRNA comprises a first stop codon “TGA” and a second stop codon selected from the group consisting of “TAA,” “TGA” and “TAG.”

7. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the mRNA has a 3’ tailing sequence of linked nucleosides selected from the group

consisting of a poly-A tail of at least 140 nucleotides, a triple helix, and a poly A-G quartet.

8. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the mRNA comprises at least one 5'terminal cap selected from the group consisting of Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

9. The isolated synthetic signal-sensor polynucleotide of claim 1, where the isolated synthetic signal-sensor polynucleotide is substantially purified.

10. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the isolated synthetic signal-sensor polynucleotide comprises at least one chemical modification.

11. The isolated synthetic signal-sensor polynucleotide of claim 10, wherein the at least one chemical modification is 1-methylpseudouridine.

12. The isolated synthetic signal-sensor polynucleotide of claim 11, further comprising the chemical modification 5-methylcytidine.

13. The isolated synthetic signal-sensor polynucleotide of claim 1, where the isolated synthetic signal-sensor polynucleotide comprises at least two chemical modifications.

14. The isolated synthetic signal-sensor polynucleotide of claim 13, wherein the modifications are located on one or more of a nucleoside and/or the backbone of said nucleotides.

15. The isolated synthetic signal-sensor polynucleotide of claim 13, where the modifications are located on both a nucleoside and a backbone linkage.

16. The isolated synthetic signal-sensor polynucleotide of claim 13, where the modifications are located on the backbone linkage.

17. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the isolated signal-sensor polynucleotide is codon optimized.

18. The isolated synthetic signal-sensor polynucleotide of claim 1, wherein the isolated signal-sensor polynucleotide is formulated.

19. The isolated synthetic signal-sensor polynucleotide of claim 1 wherein the polypeptide of interest is a factor modulating the affinity between HIF subunits and/or HIF-dependent gene expression.

20. The isolated synthetic signal-sensor polynucleotide of claim 19 wherein the HIF subunits are selected from the group consisting of SEQ ID NO: 6611-6616.

21. The isolated synthetic signal-sensor polynucleotide of claim 1 wherein the isolated synthetic signal-sensor polynucleotide comprises at least one translation enhancer element.

22. An isolated synthetic signal-sensor polynucleotide comprising:

(a) a first region of linked nucleosides, said first region encoding an oncology-related polypeptide of interest selected from the group consisting of SEQ ID NOs: 1321-2487, 6611-6616 and 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516 and 7517;

(b) a first flanking region located 5' relative to said first region comprising;

(i) a sequence of linked nucleosides selected from the group consisting of the native 5' untranslated region (UTR) of any of the nucleic acids that encode any of SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516, 7517, SEQ ID NO: 1-4 and functional variants thereof;

(c) a second flanking region located 3' relative to said first region comprising;

(i') a sequence of linked nucleosides selected from the group consisting of the native 3' UTR of any of the nucleic acids that encode any of SEQ ID NOs: 1321-2487, 6611-6616, 7355-7361, 7490, 7492, 7493, 7512, 7514, 7516, 7517, SEQ ID NO: 5-21 and functional variants thereof;

(ii') one or more sensor sequences located selected from the group consisting of the any of SEQ ID NOs: 3529-4549, SEQ ID NOs: 5571-6591 and functional variants thereof; and

(iii') a 3' tailing sequence of linked nucleosides.

23. The isolated synthetic signal-sensor polynucleotide of claim 22 wherein the first region of linked nucleosides comprises at least an open reading frame of a nucleic acid sequence, wherein the nucleic acid sequence is selected from the group consisting of SEQ ID NOs: 2488-2496, 6617-6621, 7348-7354, 7362-7489, 7491, 7494, 7506, 7511 and 7513.

24. The isolated synthetic signal-sensor polynucleotide of claim 23, wherein the open reading frame is codon optimized.

25. The isolated synthetic signal-sensor polynucleotide of claim 22, wherein the first region comprises two stop codons.

26. The isolated synthetic signal-sensor isolated polynucleotide of claim 22, wherein the first region comprises a first stop codon "TGA" and a second stop codon selected from the group consisting of "TAA," "TGA" and "TAG."

27. The isolated synthetic signal-sensor polynucleotide of claim 22, wherein the 3' tailing sequence of linked nucleosides is selected from the group consisting of a poly-A tail of at least 140 nucleotides, a triple helix, and a poly A-G quartet.

28. The isolated synthetic signal-sensor polynucleotide of claim 22, wherein the first flanking region further comprises at least one 5'terminal cap.

29. The isolated synthetic signal-sensor polynucleotide of claim 28, wherein the at least one 5′ terminal cap is selected from the group consisting of Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

30. The isolated synthetic signal-sensor polynucleotide of claim 28 where the isolated signal-sensor polynucleotide is substantially purified.

31. The isolated synthetic signal-sensor polynucleotide of claim 22, wherein the isolated synthetic signal-sensor polynucleotide comprises at least one chemical modification.

32. The isolated synthetic signal-sensor polynucleotide of claim 31, wherein the at least one chemical modification is 1-methylpseudouridine.

33. The isolated synthetic signal-sensor polynucleotide of claim 32, further comprising the chemical modification 5-methylcytidine.

34. The isolated synthetic signal-sensor polynucleotide of claim 22, comprising at least two chemical modifications in the first region.

35. The isolated synthetic signal-sensor polynucleotide of claim 34, wherein the modifications are located on one or more of a nucleoside and/or the backbone of said nucleotides.

36. The isolated synthetic signal-sensor polynucleotide of claim 34, where the modifications are located on both a nucleoside and a backbone linkage.

37. The isolated synthetic signal-sensor polynucleotide of claim 34, where the modifications are located on the backbone linkage.

38. The isolated synthetic signal-sensor polynucleotide of claim 22, where the isolated signal-sensor polynucleotide is codon optimized.

39. The isolated synthetic signal-sensor polynucleotide of claim 38, wherein the first region of linked nucleosides is codon optimized.

40. The isolated synthetic signal-sensor polynucleotide of claim 22, wherein the isolated signal-sensor polynucleotide is formulated.

41. A method of treating a disease, disorder and/or condition in a subject in need thereof by increasing the level of an oncology-related polypeptide of interest comprising administering to said subject an isolated synthetic signal-sensor polynucleotide encoding said oncology-related polypeptide.

42. A method of reducing, eliminating or preventing tumor growth in a subject in need thereof by increasing the level of an oncology-related polypeptide of interest comprising administering to said subject an isolated synthetic signal-sensor polynucleotide encoding said oncology-related polypeptide.

43. A method of reducing and/or ameliorating at least one symptom of cancer in a subject need thereof by increasing the level of an oncology-related polypeptide of

interest comprising administering to said subject an isolated synthetic signal-sensor polynucleotide encoding said oncology-related polypeptide.

44. The method of any of claims 41-43 wherein the disease, disorder and/or condition is selected from the group consisting of adrenal cortical cancer, advanced cancer, anal cancer, aplastic anemia, bileduct cancer, bladder cancer, bone cancer, bone metastasis, brain tumors, brain cancer, breast cancer, childhood cancer, cancer of unknown primary origin, Castleman disease, cervical cancer, colon/rectal cancer, endometrial cancer, esophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, renal cell carcinoma, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, liver cancer, hepatocellular carcinoma (HCC), non-small cell lung cancer, small cell lung cancer, lung carcinoid tumor, lymphoma of the skin, malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma in adult soft tissue, basal and squamous cell skin cancer, melanoma, small intestine cancer, stomach cancer, testicular cancer, throat cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor and secondary cancers caused by cancer treatment.

45. The method of claim 44 wherein the tumor growth is results from a disease, disorder and/or condition selected from the group consisting of adrenal cortical cancer, advanced cancer, anal cancer, aplastic anemia, bileduct cancer, bladder cancer, bone cancer, bone metastasis, brain tumors, brain cancer, breast cancer, childhood cancer, cancer of unknown primary origin, Castleman disease, cervical

cancer, colon/rectal cancer, endometrial cancer, esophagus cancer, Ewing family of tumors, eye cancer, gallbladder cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, gestational trophoblastic disease, Hodgkin disease, Kaposi sarcoma, renal cell carcinoma, laryngeal and hypopharyngeal cancer, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, liver cancer, hepatocellular carcinoma (HCC), non-small cell lung cancer, small cell lung cancer, lung carcinoid tumor, lymphoma of the skin, malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, oral cavity and oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma in adult soft tissue, basal and squamous cell skin cancer, melanoma, small intestine cancer, stomach cancer, testicular cancer, throat cancer, thymus cancer, thyroid cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor and secondary cancers caused by cancer treatment.

46. The method of any of claims 41-43 wherein the administration of the isolated synthetic signal-sensor polynucleotide reduces the number of cancer cells, eliminates cancer cells, prevents an increase in cancer cells and/or alleviates the symptoms of cancer in a subject.

47. The method of claim 43 wherein the at least one symptom of cancer is selected from the group consisting of weakness, aches and pains, fever, fatigue, weight loss, blood clots, increased blood calcium levels, low white blood cell count, short of breath, dizziness, headaches, hyperpigmentation, jaundice, erthema, pruritis, excessive hair growth, change in bowel habits, change in bladder function, long-lasting sores, white patches inside the mouth, white spots on the tongue, unusual bleeding or discharge, thickening or lump on parts of the body, indigestion,

trouble swallowing, changes in warts or moles, change in new skin and nagging cough and hoarseness.

48. The methods of any of claims 41-43, wherein the isolated synthetic signal-sensor polynucleotide is formulated.

49. The method of claim 48, wherein the isolated synthetic signal-sensor polynucleotide is administered at a total daily dose of between 0.001 ug and 150 ug.

50. The method of claim 49, wherein administration is by injection, topical administration, ophthalmic administration or intranasal administration.

51. The method of claim 50, wherein administration is by injection and said injection is selected from the group consisting of intradermal, subcutaneous and intramuscular.

52. The method of claim 50, wherein administration is topical administration and said topical administration is selected from the group consisting of cream, lotion, ointment, gel, spray, solution and the like.

53. A method of preferentially inducing cell death in cancer cells in a tissue or organ, comprising

(a) contacting said tissue or organ with an isolated synthetic signal-sensor polynucleotide, wherein said isolated synthetic signal-sensor polynucleotide encodes

(i) an oncology-related polypeptide whose expression triggers apoptosis or cell death, and

(ii) at least one microRNA binding site of a microRNA, where the expression of said microRNA in the cancer cell is lower than the expression of said microRNA in normal, non cancerous cells.

# FIGURE 1

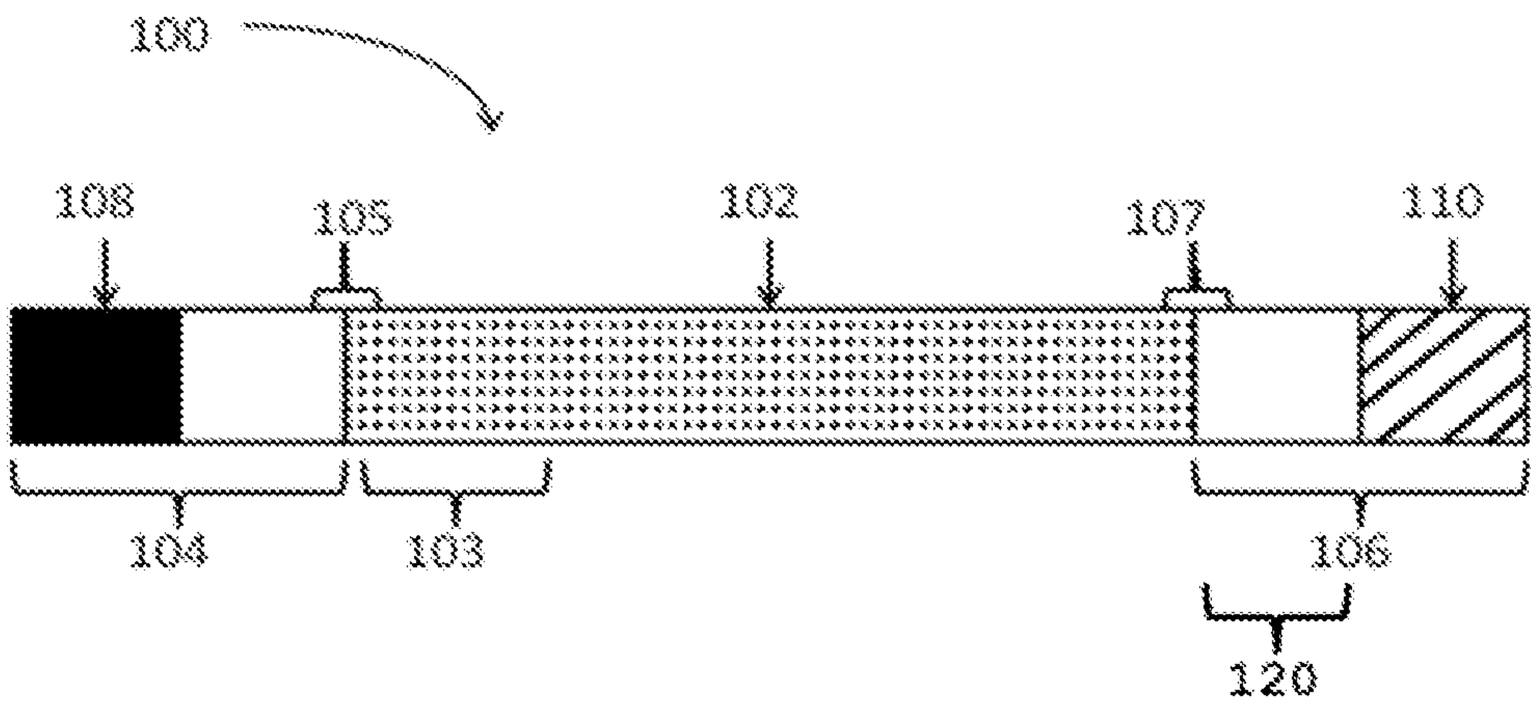
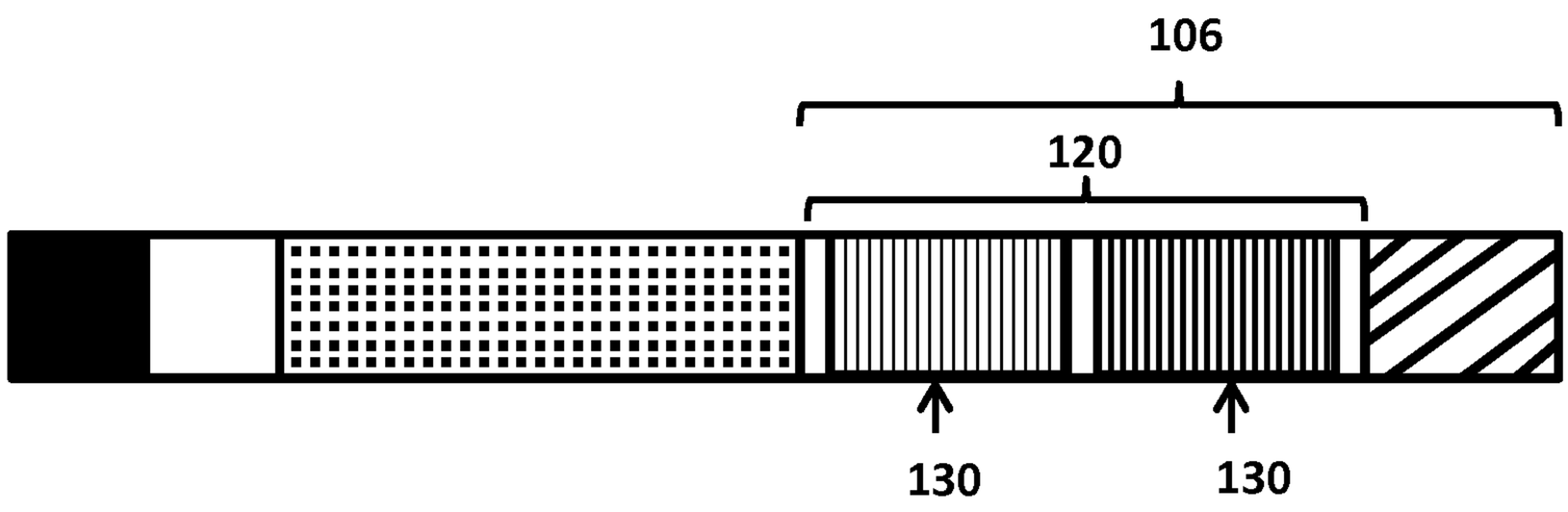
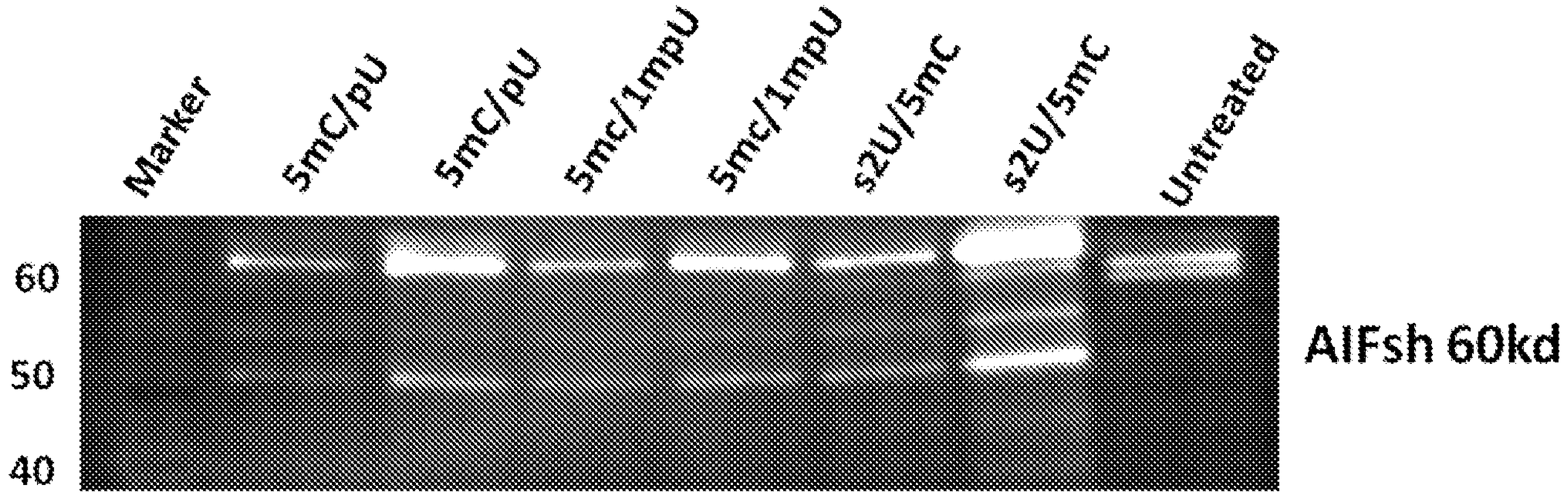


**FIGURE 2**



# FIGURE 3

**A.**


Marker
5mC/pU
5mC/pU
5mc/1mpU
5mc/1mpU
s2U/5mC
s2U/5mC
Untreated
60
50
40
AIFsh 60kd

**B.**

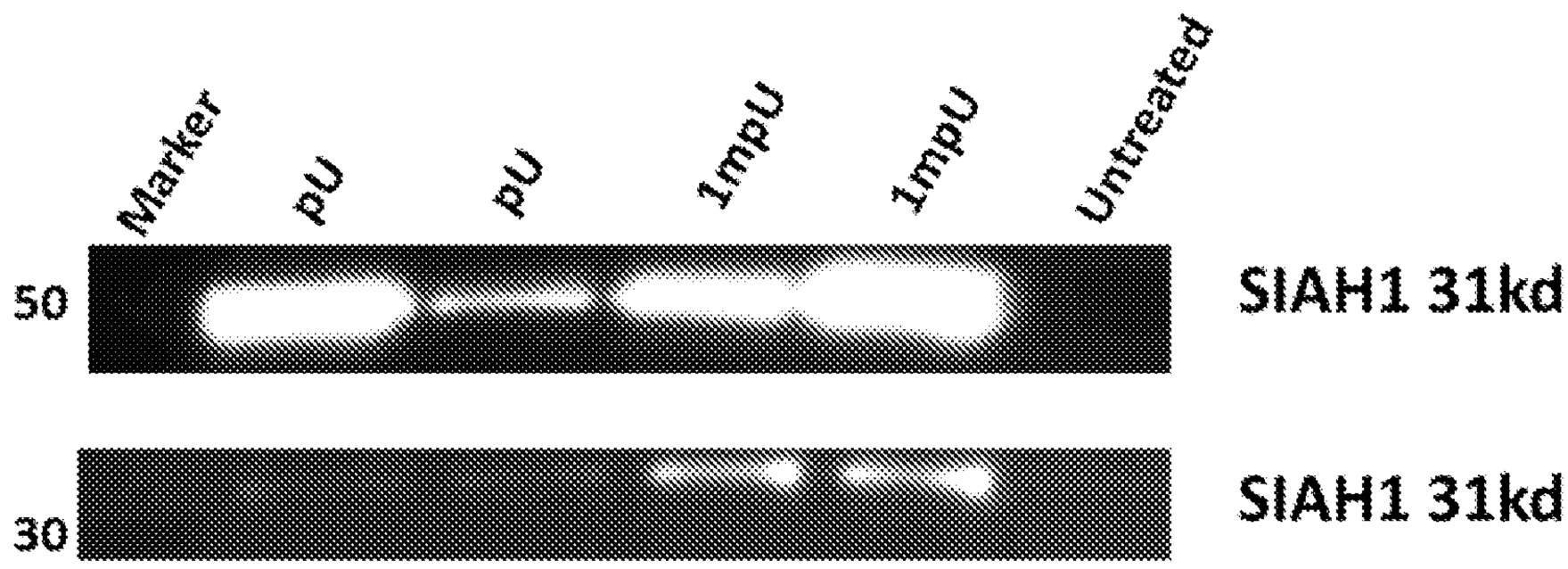

Marker
pU
pU
1mpU
1mpU
Untreated
60
50
40
AIFsh 60kd

# FIGURE 4

**A.**

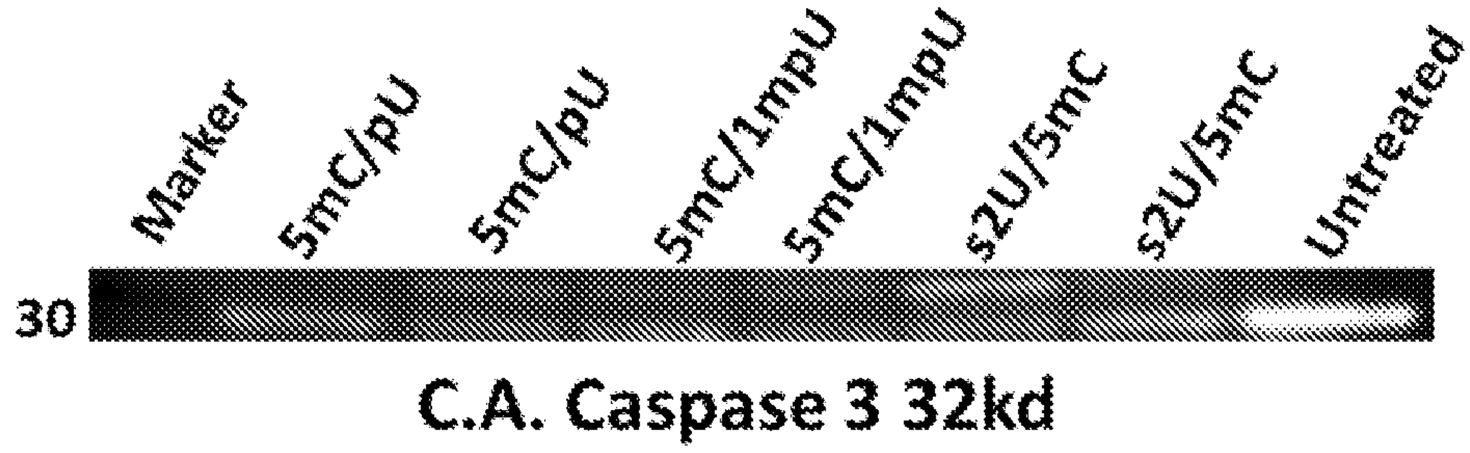

Marker
5mC/pU
5mC/pU
5mC/1mpU
5mC/1mpU
s2U/5mC
s2U/5mC
Untreated
50
SIAH1 31kd
30
SIAH1 31kd

**B.**

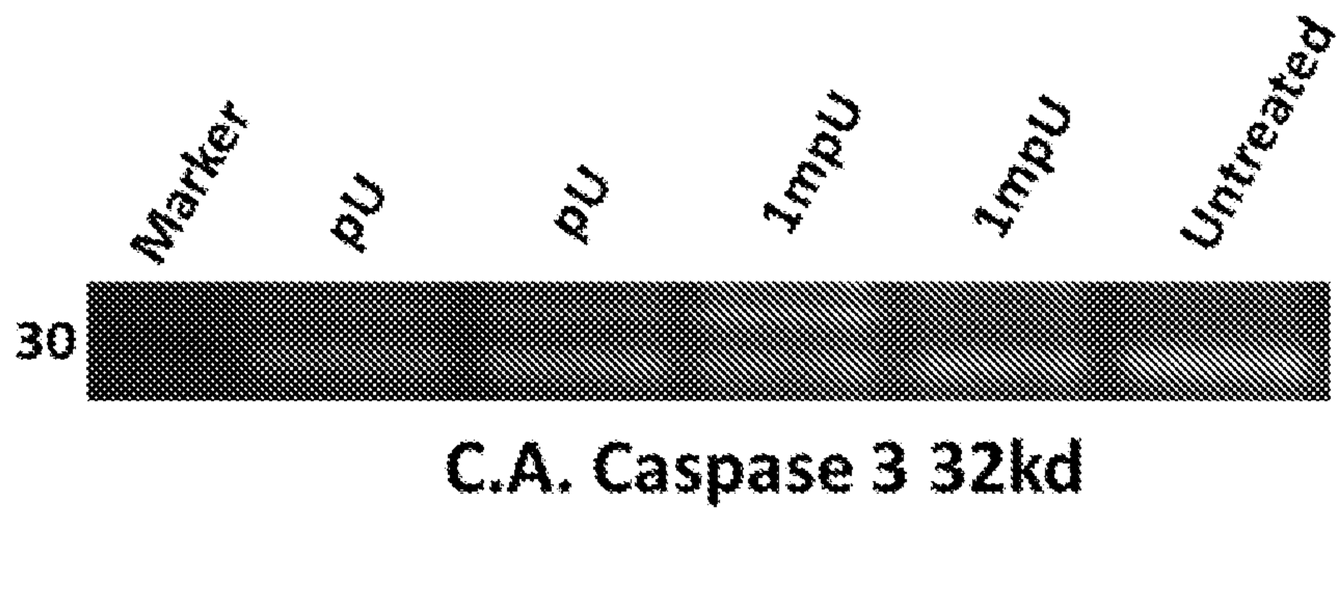

Marker
pU
pU
1mpU
1mpU
Untreated
50
SIAH1 31kd
30
SIAH1 31kd

# FIGURE 5

**A.**


Marker
5mC/pU
5mC/pU
5mC/1mpU
5mC/1mpU
s2U/5mC
s2U/5mC
Untreated
30
C.A. Caspase 3 32kd

**B.**


Marker
pU
pU
1mpU
1mpU
Untreated
30
C.A. Caspase 3 32kd

# FIGURE 6

**A.**


Marker
5mC/pU
5mC/pU
5mC/1mpU
5mC/1mpU
s2U/5mC
s2U/5mC
30
20
Granulysin 16kd

**B.**

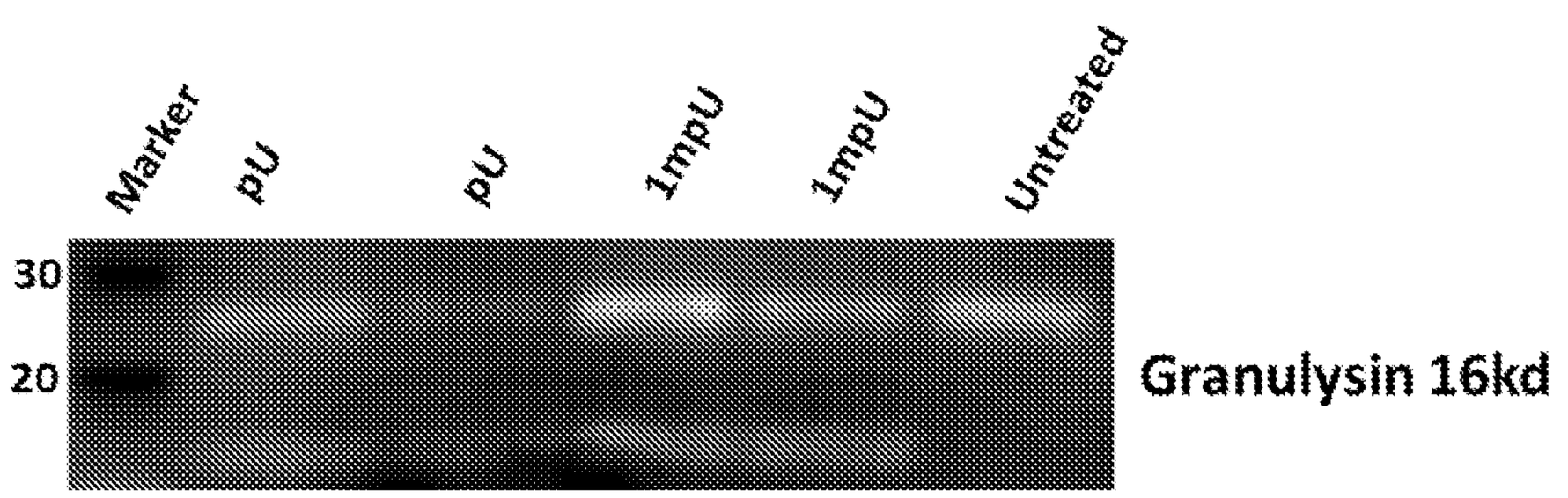
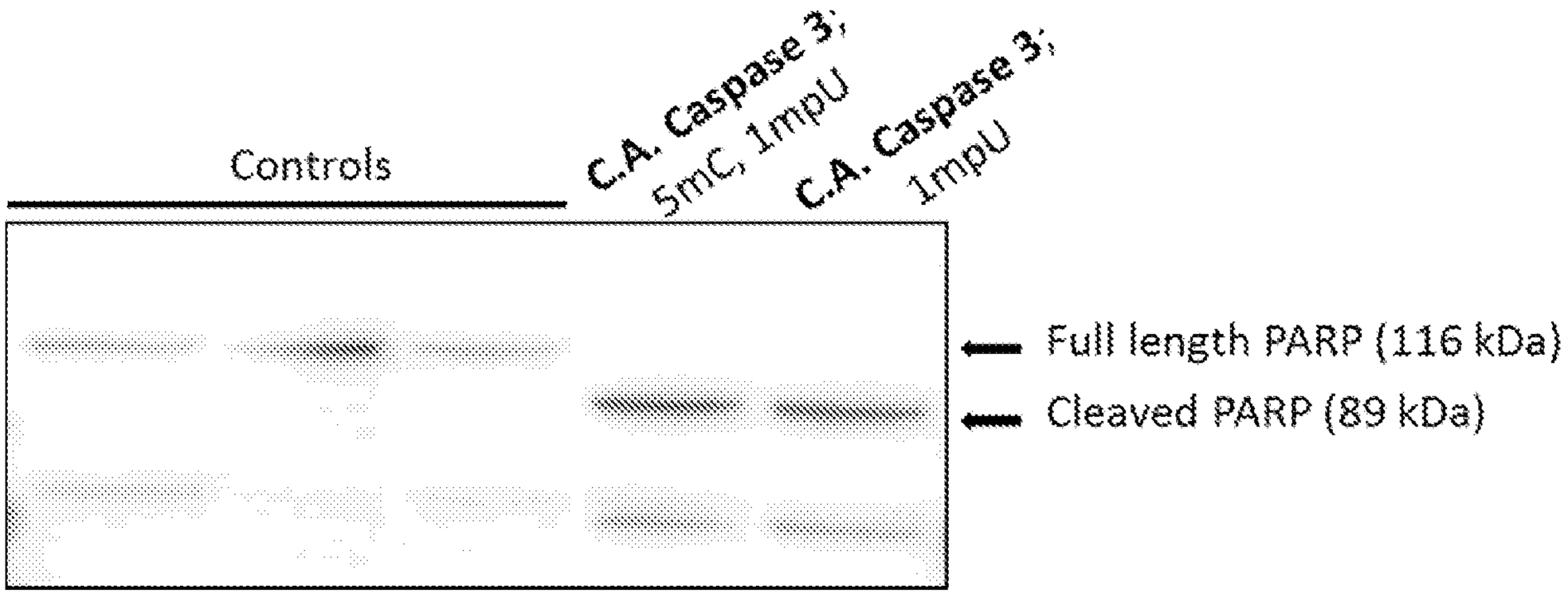
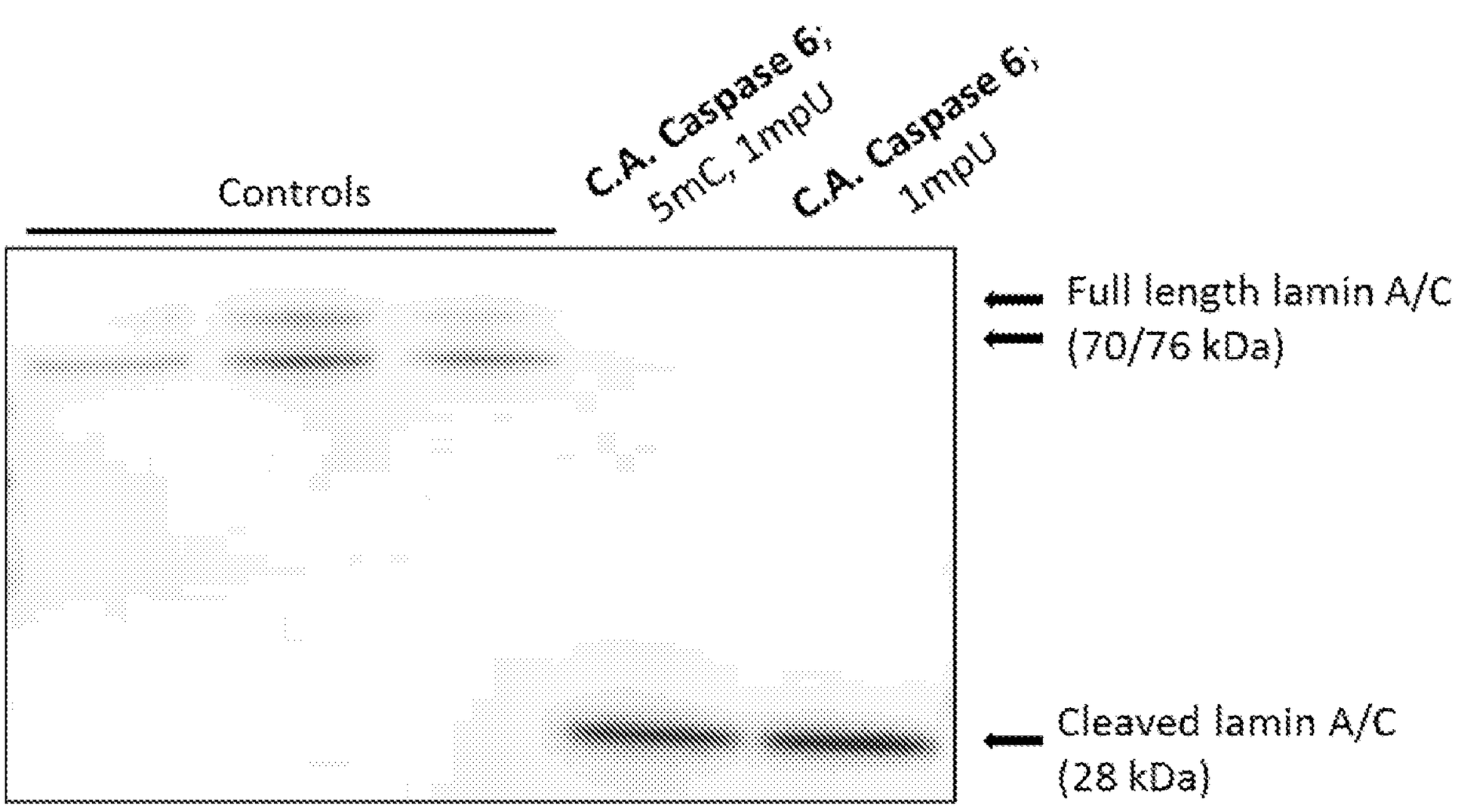

Marker
pU
pU
1mpU
1mpU
Untreated
30
20
Granulysin 16kd

**Figure 7**

**A.**


Controls
C.A. Caspase 3; 5mC, 1mpU
C.A. Caspase 3; 1mpU
Full length PARP (116 kDa)
Cleaved PARP (89 kDa)

**B.**


Controls
C.A. Caspase 6; 5mC, 1mpU
C.A. Caspase 6; 1mpU
Full length lamin A/C (70/76 kDa)
Cleaved lamin A/C (28 kDa)

# FIGURE 2