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(54) Title: MIR-15, MIR-26, MIR -31,MIR -145, MIR-147, MIR-188, MIR-215, MIR-216 MIR-331, MMU-MIR-292-3P REGULATED GENES AND PATHWAYS AS TARGETS FOR THERAPEUTIC INTERVENTION

(57) Abstract: The present invention concerns methods and compositions for identifying genes or genetic pathways modulated by miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR- 215, miR-216, miR-331, mmu-miR-292-3p, and using nucleic acid comprising all or part of the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, mmu-miR-292-3p sequences to modulate a gene or gene pathway, using this profile in assessing the condition of a patient and/or treating the patient with an appropriate miRNA.

DESCRIPTION

MIR-15, MIR -26, MIR -31, MIR -145, MIR -147, MIR -188, MIR -215, MIR -216, MIR -331, MMU-MIR-292-3p REGULATED GENES AND PATHWAYS AS TARGETS FOR THERAPEUTIC INTERVENTION

BACKGROUND OF THE INVENTION

This application claims the benefit of priority to U.S. Provisional Patent Application Serial No. 60/948,350 filed July 6, 2007 and U.S. Provisional Patent Application Serial No. 60/826,173 filed September 19, 2006, which are hereby incorporated by reference in their entirety.

I. FIELD OF THE INVENTION

The present invention relates to the fields of molecular biology and medicine. More specifically, the invention relates to methods and compositions for the treatment of diseases or conditions that are affected by microRNA (miRNA) miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p expression or lack thereof, and genes and cellular pathways directly and indirectly modulated by such.

II. BACKGROUND

In 2001, several groups used a cloning method to isolate and identify a large group of "microRNAs" (miRNAs) from *C. elegans*, *Drosophila*, and humans (Lagos-Quintana *et al.*, 2001; Lau *et al.*, 2001; Lee and Ambros, 2001). Several hundreds of miRNAs have been identified in plants and animals—including humans—which do not appear to have endogenous siRNAs. Thus, while similar to siRNAs, miRNAs are distinct.

miRNAs thus far observed have been approximately 21-22 nucleotides in length, and they arise from longer precursors, which are transcribed from non-protein-encoding genes. See review of Carrington and Ambros (2003). The precursors form structures that fold back on themselves in self-complementary regions; they are then processed by the nuclease Dicer (in animals) or DCL1 (in plants) to generate the short double-stranded miRNA. One of the miRNA strands is incorporated into a complex of proteins and miRNA called the RNA-induced silencing complex (RISC). The miRNA guides the RISC complex to a target mRNA, which is then cleaved or

translationally silenced, depending on the degree of sequence complementarity of the miRNA to its target mRNA. Currently, it is believed that perfect or nearly perfect complementarity leads to mRNA degradation, as is most commonly observed in plants. In contrast, imperfect base pairing, as is primarily found in animals, leads to translational silencing. However, recent data suggest additional complexity (Bagga *et al.*, 2005; Lim *et al.*, 2005), and mechanisms of gene silencing by miRNAs remain under intense study.

Recent studies have shown that changes in the expression levels of numerous miRNAs are associated with various cancers (reviewed in Esquela-Kerscher and Slack, 2006; Calin and Croce, 2006). miRNAs have also been implicated in regulating cell growth and cell and tissue differentiation - cellular processes that are associated with the development of cancer.

The inventors previously demonstrated that the microRNAs described in this application are involved with the regulation of numerous cell activities that represent intervention points for cancer therapy and for therapy of other diseases and disorders (U.S. Patent Applications serial number 11/141,707 filed May 31, 2005 and serial number 11/273,640 filed November 14, 2005). For example, cell proliferation, cell division, and cell survival are frequently altered in human cancers. Overexpression of hsa-miR-147, -215 or mmu-miR-292-3p decreases the proliferation and/or viability of certain normal or cancerous cell lines. Overexpression of hsa-miR-216 increases the proliferation of normal skin and lung cancer cells. Overexpression of hsa-miR-15a, -26a, -145, -188 or -331 can inhibit or stimulate proliferation or viability of certain normal or cancerous cell lines, depending on the individual cell type. Similarly, the inventors previously observed that miRNA inhibitors of hsa-miR-215, -216, and -331 reduce proliferation of certain cell lines, and miRNA inhibitors of hsa-miR-15a increase proliferation of skin basal cell carcinoma cells. Apoptosis, programmed cell death, is frequently disrupted in cancers. Insufficient apoptosis results in uncontrolled cell proliferation, a hallmark of cancer. The inventors observed that overexpression of hsa-miR-31, -15a, -147, -215, -331 increase apoptosis; overexpression of hsa-miR-145, hsa-miR-216, or mmu-miR-292-3p decrease apoptosis in various cancer cell lines. Overexpression of hsa-miR-26a or -188 induces or suppresses apoptosis, depending on the cell type.

More than 90% of human cancer samples have active telomerase (Dong *et al,*.2005); whereas most terminally-differentiated cells lack telomerase. The hTert gene encodes the catalytic domain of telomerase. The inventors previously observed that hsa-miR-15a, hsa -26a, and hsa -147 activate the hTert gene in normal human fibroblasts. Such activity might contribute to cancer by activating telomerase.

These data suggest that expression or lack of expression of a specific miRNA in certain cells could likely contribute to cancer and other diseases. The inventors have also previously observed associations between miRNA expression and certain human cancers. For example, hsa-miR-145, -188, and -331 are expressed at significantly lower levels in the tumors of most lung cancer patients than in lung tissues from patients without disease. Hsa-mir-145 and -331 are also expressed at lower levels in colon tumors, but hsa-miR-31 is expressed at higher levels in colon tumors than in normal colon tissues. Hsa-mir-15a is expressed at higher levels in cancerous breast, prostate, and thyroid tissues than in corresponding normal tissues. Hsa-miR-145 is expressed at lower levels in colon, breast, and bladder cancers than in corresponding normal tissues. microRNAs described in this application were also previously observed by the inventors to be differentially expressed in tissues from patients with prion disease, lupus, multiple sclerosis, or Alzheimer's disease.

Bioinformatics analyses suggest that any given miRNA may bind to and alter the expression of up to several hundred different genes. In addition, a single gene may be regulated by several miRNAs. Thus, each miRNA may regulate a complex interaction among genes, gene pathways, and gene networks. Mis-regulation or alteration of these regulatory pathways and networks, involving miRNAs, are likely to contribute to the development of disorders and diseases such as cancer. Although bioinformatics tools are helpful in predicting miRNA binding targets, all have limitations. Because of the imperfect complementarity with their target binding sites, it is difficult to accurately predict the mRNA targets of miRNAs with bioinformatics tools alone. Furthermore, the complicated interactive regulatory networks among miRNAs and target genes make it difficult to accurately predict which genes will actually be mis-regulated in response to a given miRNA.

Correcting gene expression errors by manipulating miRNA expression or by repairing miRNA mis-regulation represent promising methods to repair genetic

disorders and cure diseases like cancer. A current, disabling limitation of this approach is that, as mentioned above, the details of the regulatory pathways and gene networks that are affected by any given miRNA, have been largely unknown. This represents a significant limitation for treatment of cancers in which a specific miRNA may play a role. A need exists to identify the genes, genetic pathways, and genetic networks that are regulated by or that may regulate expression of miRNAs.

SUMMARY OF THE INVENTION

The present invention provides additional compositions and methods by identifying genes that are direct targets for miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p regulation or that are indirect or downstream targets of regulation following the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p-mediated modification of another gene(s) expression. Furthermore, the invention describes gene, disease, and/or physiologic pathways and networks that are influenced by miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p and their family members. In certain aspects, compositions of the invention are administered to a subject having, suspected of having, or at risk of developing a metabolic, an immunologic, an infectious, a cardiovascular, a digestive, an endocrine, an ocular, a genitourinary, a blood, a musculoskeletal, a nervous system, a congenital, a respiratory, a skin, or a cancerous disease or condition.

In particular aspects, a subject or patient may be selected for treatment based on expression and/or aberrant expression of one or more miRNA or mRNA. In a further aspect, a subject or patient may be selected for treatment based on aberrations in one or more biologic or physiologic pathway(s), including aberrant expression of one or more gene associated with a pathway, or the aberrant expression of one or more protein encoded by one or more gene associated with a pathway. In still a further aspect, a subject or patient may be selected based on aberrations in miRNA expression, or biologic and/or physiologic pathway(s). A subject may be assessed for sensitivity, resistance, and/or efficacy of a therapy or treatment regime based on the evaluation and/or analysis of miRNA or mRNA expression or lack thereof. A subject may be evaluated for amenability to certain therapy prior to, during, or after administration of one or therapy to a subject or patient. Typically, evaluation or

assessment may be done by analysis of miRNA and/or mRNA, as well as combination of other assessment methods that include but are not limited to histology, immunohistochemistry, blood work, etc.

In some embodiments, an infectious disease or condition includes a bacterial, viral, parasite, or fungal infection. Many of these genes and pathways are associated with various cancers and other diseases. Cancerous conditions include, but are not limited to astrocytoma, acute myeloid leukemia, anaplastic large cell lymphoma, acure lymphoblastic leukemia, angiosarcoma, B-cell pymphoma, Burkitt's lymphoma, breast carcinoma, bladder carcinoma, carcinoma of the head and neck, cervical carcinoma, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, Ewing's sarcoma, fibrosarcoma, glioma, glioblastoma, gastrinoma, gastric carcinoma, hepatoblastoma, hepatocellular carcinoma, Kaposi's sarcoma, Hodgkin lymphoma, laryngeal squamous cell carcinoma, larynx carcinoma, leukemia, leiomyosarcoma, lipoma, liposarcoma, melanoma, mantle cell lymphoma, medulloblastoma, mesothelioma, myxofibrosarcoma, myeloid leukemia, mucosa-associated lymphoid tissue B cell lymphoma, multiple myeloma, high-risk myelodysplastic syndrome, nasopharyngeal carcinaoma, neuroblastoma, neurofibroma, high-grade non-Hodgkin lymphoma, non-hodgkin lymphoma, lung carcinoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, pheochromocytoma, prostate carcinoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland tumor, Schwanomma, small cell lung cancer, squamous cell carcinoma of the head and neck, testicular tumor, thyroid carcinoma, urothelial carcinoma, and wilm's tumor, wherein the modulation of one or more gene is sufficient for a therapeutic response. Typically a cancerous condition is an aberrant hyperproliferative condition associated with the uncontrolled growth or inability to undergo cell death, including apoptosis.

The present invention provides methods and compositions for identifying genes that are direct targets for miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p regulation or that are downstream targets of regulation following the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p-mediated

modification of upstream gene expression. Furthermore, the invention describes gene pathways and networks that are influenced by miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p expression. Many of these genes and pathways are associated with various cancers and other diseases. The altered expression or function of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p in cells would lead to changes in the expression of these key genes and contribute to the development of disease or other conditions. Introducing miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p (for diseases where the miRNA is down-regulated) or a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor (for diseases where the miRNA is up-regulated) into diseased or abnormal cells or tissues or subjects would result in a therapeutic response. The identities of key genes that are regulated directly or indirectly by miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p and the disease with which they are associated are provided herein. In certain aspects a cell may be an epithelial, an endothelial, a mesothelial, a glial, a stromal, or a mucosal cell. The cell can be, but is not limited to a brain, a neuronal, a blood, an endometrial, a meninges, an esophageal, a lung, a cardiovascular, a liver, a lymphoid, a breast, a bone, a connective tissue, a fat, a retinal, a thyroid, a glandular, an adrenal, a pancreatic, a stomach, an intestinal, a kidney, a bladder, a colon, a prostate, a uterine, an ovarian, a cervical, a testicular, a splenic, a skin, a smooth muscle, a cardiac muscle, or a striated muscle cell.

In certain aspects, the cell, tissue, or target may not be defective in miRNA expression yet may still respond therapeutically to expression or over expression of a miRNA. miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p could be used as a therapeutic target for any of these diseases. In certain embodiments miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p can be used to modulate the activity of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p in a subject, organ, tissue, or cell.

A cell, tissue, or subject may be a cancer cell, a cancerous tissue, harbor cancerous tissue, or be a subject or patient diagnosed or at risk of developing a disease or condition. In certain aspects a cell may be an epithelial, an endothelial, a mesothelial, a glial, a stromal, or a mucosal cell. The cell can be, but is not limited to a brain, a neuronal, a blood, an endometrial, a meninges, an esophageal, a lung, a cardiovascular, a liver, a lymphoid, a breast, a bone, a connective tissue, a fat, a retinal, a thyroid, a glandular, an adrenal, a pancreatic, a stomach, an intestinal, a kidney, a bladder, a colon, a prostate, a uterine, an ovarian, a cervical, a testicular, a splenic, a skin, a smooth muscle, a cardiac muscle, or a striated muscle cell. In still a further aspect cancer includes, but is not limited to astrocytoma, acute myeloid leukemia, anaplastic large cell lymphoma, acute lymphoblastic leukemia, angiosarcoma, B-cell lymphoma, Burkitt's lymphoma, breast carcinoma, bladder carcinoma, carcinoma of the head and neck, cervical carcinoma, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, Ewing's sarcoma, fibrosarcoma, glioma, glioblastoma, gastrinoma, gastric carcinoma, hepatoblastoma, hepatocellular carcinoma, Kaposi's sarcoma, Hodgkin lymphoma, laryngeal squamous cell carcinoma, larynx carcinoma, leukemia, leiomyosarcoma, lipoma, liposarcoma, melanoma, mantle cell lymphoma, medulloblastoma, mesothelioma, myxofibrosarcoma, myeloid leukemia, mucosa-associated lymphoid tissue B cell lymphoma, multiple myeloma, high-risk myelodysplastic syndrome, nasopharyngeal carcinoma, neuroblastoma, neurofibroma, high-grade non-Hodgkin lymphoma, non-Hodgkin lymphoma, lung carcinoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, pheochromocytoma, prostate carcinoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland tumor, Schwanomma, small cell lung cancer, squamous cell carcinoma of the head and neck, testicular tumor, thyroid carcinoma, urothelial carcinoma, and Wilm's tumor.

Embodiments of the invention include methods of modulating gene expression, or biologic or physiologic pathways in a cell, a tissue, or a subject comprising administering to the cell, tissue, or subject an amount of an isolated nucleic acid or mimetic thereof comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid,

mimetic, or inhibitor sequence in an amount sufficient to modulate the expression of a gene positively or negatively modulated by a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p miRNA. A "miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence" or "miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor" includes the full length precursor of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or complement thereof or processed (*i.e.,* mature) sequence of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p and related sequences set forth herein, as well as 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more nucleotides of a precursor miRNA or its processed sequence, or complement thereof, including all ranges and integers there between. In certain embodiments, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor contains the full-length processed miRNA sequence or complement thereof and is referred to as the "miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p full-length processed nucleic acid sequence" or "miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p full-length processed inhibitor sequence." In still further aspects, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid comprises at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 50 nucleotide (including all ranges and integers there between) segment or complementary segment of a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p that is at least 75, 80, 85, 90, 95, 98, 99 or 100% identical to SEQ ID NO:1 to SEQ ID NO:391. The general terms miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p includes all members of the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p family that share at least part of a mature miRNA sequence.

Mature miR-15 sequences include: hsa-miR-15a, UAGCAGCACAUAAUGGUUUGUG, MIMAT0000068, SEQ ID NO:1); hsa-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0000417, SEQ ID NO:2); hsa-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0000069, SEQ ID NO:3); hsa-miR-195, UAGCAGCACAGAAAUAUUGGC (MIMAT0000461, SEQ ID NO:4); age-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002638, SEQ ID NO:5); age-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002203, SEQ ID NO:6); age-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002639, SEQ ID NO:7); bta-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0003792, SEQ ID NO:8); bta-miR-16, UAGCAGCACGUAAAUAUUGGC (MIMAT0003525, SEQ ID NO:9); dre-miR-15a, UAGCAGCACAGAAUGGUUUGUG (MIMAT0001772, SEQ ID NO:10); dre-miR-15a*, CAGGCCGUACUGUGCUGCGGCA (MIMAT0003395, SEQ ID NO:11); dre-miR-15b, UAGCAGCACAUCAUGGUUUGUA (MIMAT0001773, SEQ ID NO:12); dre-miR-15c, AAGCAGCGCGUCAUGGUUUUC (MIMAT0003764, SEQ ID NO:13); dre-miR-16a, UAGCAGCACGUAAAUAUUGGUG (MIMAT0001774, SEQ ID NO:14); dre-miR-16b, UAGCAGCACGUAAAUAUUGGAG (MIMAT0001775, SEQ ID NO:15); dre-miR-16c, UAGCAGCAUGUAAAUAUUGGAG (MIMAT0001776, SEQ ID NO:16); dre-miR-457a, AAGCAGCACAUCAAUAUUGGCA (MIMAT0001883, SEQ ID NO:17); dre-miR-457b, AAGCAGCACAUAAAUACUGGAG (MIMAT0001884, SEQ ID NO:18); fru-miR-15a, UAGCAGCACGGAAUGGUUUGUG (MIMAT0003105, SEQ ID NO:19); fru-miR-15b, UAGCAGCGCAUCAUGGUUUGUA (MIMAT0003085, SEQ ID NO:20); fru-miR-16, UAGCAGCACGUAAAUAUUGGAG (MIMAT0003107, SEQ ID NO:21); gga-miR-15a, UAGCAGCACAUAAUGGUUUGU (MIMAT0001117, SEQ ID NO:22); gga-miR-15b, UAGCAGCACAUCAUGGUUUGCA (MIMAT0001154, SEQ ID NO:23); gga-miR-16, UAGCAGCACGUAAAUAUUGGUG (MIMAT0001116, SEQ ID NO:24); ggo-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002640, SEQ ID NO:25); ggo-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002202, SEQ ID NO:26); ggo-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002641, SEQ ID NO:27); ggo-miR-195, UAGCAGCACAGAAAUAUUGGC (MIMAT0002316, SEQ ID NO:28); lca-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002648, SEQ ID NO:29);

lca-miR-16, UAGCAGCACGUAAAUAUUGGUG (MIMAT0002649, SEQ ID NO:30); lla-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002656, SEQ ID NO:31); lla-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002208, SEQ ID NO:32); lla-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002657, SEQ ID NO:33); mdo-miR-15a, UAGCAGCACAUAAUGGUUUGUU (MIMAT0004144, SEQ ID NO:34); mdo-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0004145, SEQ ID NO:35); mml-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002650, SEQ ID NO:36); mml-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002207, SEQ ID NO:37); mml-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002651, SEQ ID NO:38); mmu-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0000526, SEQ ID NO:39); mmu-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0000124, SEQ ID NO:40); mmu-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0000527, SEQ ID NO:41); mmu-miR-195, UAGCAGCACAGAAAUAUUGGC (MIMAT0000225, SEQ ID NO:42); mne-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002642, SEQ ID NO:43); mne-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002209, SEQ ID NO:44); mne-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002643, SEQ ID NO:45); ppa-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002646, SEQ ID NO:46); ppa-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002204, SEQ ID NO:47); ppa-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002647, SEQ ID NO:48); ppa-miR-195, UAGCAGCACAGAAAUAUUGGC (MIMAT0002317, SEQ ID NO:49); ppy-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002652, SEQ ID NO:50); ppy-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002205, SEQ ID NO:51); ppy-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002653, SEQ ID NO:52); ptr-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002654, SEQ ID NO:53); ptr-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0002206, SEQ ID NO:54); ptr-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002655, SEQ ID NO:55); rno-miR-15b, UAGCAGCACAUCAUGGUUUACA (MIMAT0000784, SEQ ID NO:56); rno-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0000785, SEQ ID NO:57); rno-miR-195, UAGCAGCACAGAAAUAUUGGC (MIMAT0000870, SEQ ID

NO:58); sla-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0002644, SEQ ID NO:59); sla-miR-16, UAGCAGCACGUAAAUAUUGGCG (MIMAT0002645, SEQ ID NO:60); ssc-miR-15b, CCGCAGCACAUCAUGGUUUACA (MIMAT0002125, SEQ ID NO:61); tni-miR-15a, UAGCAGCACGGAAUGGUUUGUG (MIMAT0003106, SEQ ID NO:62); tni-miR-15b, UAGCAGCGCAUCAUGGUUUGUA (MIMAT0003086, SEQ ID NO:63); tni-miR-16, UAGCAGCACGUAAAUAUUGGAG (MIMAT0003108, SEQ ID NO:64); xtr-miR-15a, UAGCAGCACAUAAUGGUUUGUG (MIMAT0003560, SEQ ID NO:65); xtr-miR-15b, UAGCAGCACAUCAUGAUUUGCA (MIMAT0003561, SEQ ID NO:66); xtr-miR-15c, UAGCAGCACAUCAUGGUUUGUA (MIMAT0003651, SEQ ID NO:67); xtr-miR-16a, UAGCAGCACGUAAAUAUUGGUG (MIMAT0003563, SEQ ID NO:68); xtr-miR-16b, UAGCAGCACGUAAAUAUUGGGU (MIMAT0003668, SEQ ID NO:69); xtr-miR-16c, UAGCAGCACGUAAAUACUGGAG (MIMAT0003562, SEQ ID NO:70); or a complement thereof.

Mature miR-26 sequences include: hsa-miR-26a, UUCAAGUAAUCCAGGAUAGGC (MIMAT0000082, SEQ ID NO:71); hsa-miR-26b, UUCAAGUAAUUCAGGAUAGGUU (MIMAT0000083, SEQ ID NO:72); bta-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0003516, SEQ ID NO:73); bta-miR-26b, UUCAAGUAAUUCAGGAUAGGUU (MIMAT0003531, SEQ ID NO:74); dre-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0001794, SEQ ID NO:75); dre-miR-26b, UUCAAGUAAUCCAGGAUAGGUU (MIMAT0001795, SEQ ID NO:76); fru-miR-26, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0003037, SEQ ID NO:77); gga-miR-26a, UUCAAGUAAUCCAGGAUAGGC (MIMAT0001118, SEQ ID NO:78); ggo-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002345, SEQ ID NO:79); lla-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002347, SEQ ID NO:80); mml-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002349, SEQ ID NO:81); mmu-miR-26a, UUCAAGUAAUCCAGGAUAGGC (MIMAT0000533, SEQ ID NO:82); mmu-miR-26b, UUCAAGUAAUUCAGGAUAGGUU (MIMAT0000534, SEQ ID NO:83); mne-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002348, SEQ ID NO:84); ppa-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002350, SEQ ID NO:85); ppy-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002346, SEQ ID NO:86); ptr-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002344, SEQ ID NO:87); rno-miR-26a, UUCAAGUAAUCCAGGAUAGGC (MIMAT0000796, SEQ ID NO:88); rno-miR-

26b, UUCAAGUAAUUCAGGAUAGGUU (MIMAT0000797, SEQ ID NO:89); ssc-miR-26a, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0002135, SEQ ID NO:90); tni-miR-26, UUCAAGUAAUCCAGGAUAGGCU (MIMAT0003038, SEQ ID NO:91); xtr-miR-26, UUCAAGUAAUCCAGGAUAGGC (MIMAT0003569, SEQ ID NO:92), or a complement thereof.

Mature miR-31 sequences include: hsa-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0000089, SEQ ID NO:93); bmo-miR-31, GGCAAGAAGUCGGCAUAGCUG, (MIMAT0004213, SEQ ID NO:94); bta-miR-31, AGGCAAGAUGCUGGCAUAGCU, (MIMAT0003548, SEQ ID NO:95); dme-miR-31a, UGGCAAGAUGUCGGCAUAGCUGA, (MIMAT0000400, SEQ ID NO:96); dme-miR-31b, UGGCAAGAUGUCGGAAUAGCUG, (MIMAT0000389, SEQ ID NO:97); dps-miR-31a, UGGCAAGAUGUCGGCAUAGCUGA, (MIMAT0001220, SEQ ID NO:98); dps-miR-31b, UGGCAAGAUGUCGGAAUAGCUGA, (MIMAT0001221, SEQ ID NO:99); dre-miR-31, GGCAAGAUGUUGGCAUAGCUG, (MIMAT0003347, SEQ ID NO:100); gga-miR-31, AGGCAAGAUGUUGGCAUAGCUG, (MIMAT0001189, SEQ ID NO:101); ggo-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002381, SEQ ID NO:102); mdo-miR-31, GGAGGCAAGAUGUUGGCAUAGCUG, (MIMAT0004094, SEQ ID NO:103); mml-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002379, SEQ ID NO:104); mmu-miR-31, AGGCAAGAUGCUGGCAUAGCUG, (MIMAT0000538, SEQ ID NO:105); mne-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002383, SEQ ID NO:106); ppa-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002384, SEQ ID NO:107); ppy-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002382, SEQ ID NO:108); ptr-miR-31, GGCAAGAUGCUGGCAUAGCUG, (MIMAT0002380, SEQ ID NO:109); rno-miR-31, AGGCAAGAUGCUGGCAUAGCUG, (MIMAT0000810, SEQ ID NO:110); sme-miR-31b, AGGCAAGAUGCUGGCAUAGCUGA, (MIMAT0003980, SEQ ID NO:111); xtr-miR-31, AGGCAAGAUGUUGGCAUAGCUG, (MIMAT0003679, SEQ ID NO:112) or a complement thereof.

Mature miR-145 sequences include: hsa-miR-145 GUCCAGUUUUCCCAGGAAUCCCUU (MIMAT0000437, SEQ ID NO:113), or a complement thereof.

Mature miR-147 sequences include: hsa-miR-147 GUGUGUGGAAAUGCUUCUGC (MIMAT0000251, SEQ ID NO:114) , or a complement thereof.

Mature miR-188 sequences include: hsa-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0000457, SEQ ID NO:115); hsa-miR-532, CAUGCCUUGAGUGUAGGACCGU (MIMAT0002888, SEQ ID NO:116); bta-miR-532, CAUGCCUUGAGUGUAGGACCGU (MIMAT0003848, SEQ ID NO:117); hsa-miR-660, UACCCAUUGCAUAUCGGAGUUG (MIMAT0003338, SEQ ID NO:118); mml-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0002307, SEQ ID NO:119); mmu-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0000217, SEQ ID NO:120); mmu-miR-532, CAUGCCUUGAGUGUAGGACCGU (MIMAT0002889, SEQ ID NO:121); mne-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0002310, SEQ ID NO:122); ppa-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0002311, SEQ ID NO:123); ppy-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0002309, SEQ ID NO:124); or ptr-miR-188, CAUCCCUUGCAUGGUGGAGGGU (MIMAT0002308, SEQ ID NO:125) , or a complement thereof.

Mature miR-215 sequences include: hsa-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0000272, SEQ ID NO:126); hsa-miR-192, CUGACCUAUGAAUUGACAGCC (MIMAT0000222, SEQ ID NO:127); bta-miR-192, CUGACCUAUGAAUUGACAGCCAG (MIMAT0003820, SEQ ID NO:128); bta-miR-215, AUGACCUAUGAAUUGACAGACA (MIMAT0003797, SEQ ID NO:129); dre-miR-192, AUGACCUAUGAAUUGACAGCC (MIMAT0001275, SEQ ID NO:130); fru-miR-192, AUGACCUAUGAAUUGACAGCC (MIMAT0002941, SEQ ID NO:131); gga-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0001134, SEQ ID NO:132); ggo-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0002734, SEQ ID NO:133); mml-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0002728, SEQ ID NO:134); mmu-miR-192, CUGACCUAUGAAUUGACA (MIMAT0000517, SEQ ID NO:135); mmu-miR-215, AUGACCUAUGAUUUGACAGAC (MIMAT0000904, SEQ ID NO:136); mne-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0002736, SEQ ID NO:137); ppy-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0002732, SEQ ID NO:138); ptr-miR-215, AUGACCUAUGAAUUGACAGAC (MIMAT0002730, SEQ ID NO:139); rno-miR-192, CUGACCUAUGAAUUGACAGCC (MIMAT0000867, SEQ ID NO:140);

rno-miR-215, AUGACCUAUGAUUUGACAGAC (MIMAT0003118, SEQ ID NO:141); tni-miR-192, AUGACCUAUGAAUUGACAGCC (MIMAT0002942, SEQ ID NO:142); xtr-miR-192, AUGACCUAUGAAUUGACAGCC (MIMAT0003615, SEQ ID NO:143); or xtr-miR-215, AUGACCUAUGAAAUGACAGCC (MIMAT0003628, SEQ ID NO:144) , or a complement thereof.

Mature miR-216 sequences include: hsa-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0000273, SEQ ID NO:145); dre-miR-216a, UAAUCUCAGCUGGCAACUGUGA, (MIMAT0001284, SEQ ID NO:146); dre-miR-216b, UAAUCUCUGCAGGCAACUGUGA, (MIMAT0001867, SEQ ID NO:147); fru-miR-216a, AAAUCUCAGCUGGCAACUGUGA, (MIMAT0002973, SEQ ID NO:148); fru-miR-216b, UAAUCUCUGCAGGCAACUGUGA, (MIMAT0002975, SEQ ID NO:149); gga-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0001131, SEQ ID NO:150); ggo-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0002560, SEQ ID NO:151); lca-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0002558, SEQ ID NO:152); mdo-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0004131, SEQ ID NO:153); mmu-miR-216a, UAAUCUCAGCUGGCAACUGUG, (MIMAT0000662, SEQ ID NO:154); mmu-miR-216b, GGGAAAUCUCUGCAGGCAAAUGUGA, (MIMAT0003729, SEQ ID NO:155); ppa-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0002562, SEQ ID NO:156); ppy-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0002561, SEQ ID NO:157); ptr-miR-216, UUAUCUCAGCUGGCAACUGUG, (MIMAT0002559, SEQ ID NO:158); rno-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0000886, SEQ ID NO:159); ssc-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0002130, SEQ ID NO:160); tni-miR-216a, AAAUCUCAGCUGGCAACUGUGA, (MIMAT0002974, SEQ ID NO:161); tni-miR-216b, UAAUCUCUGCAGGCAACUGUGA, (MIMAT0002976, SEQ ID NO:162); or xtr-miR-216, UAAUCUCAGCUGGCAACUGUG, (MIMAT0003629, SEQ ID NO:163).

Mature miR-331 sequences include hsa-miR-331 GCCCCUGGGCCUAUCCUAGAA (MIMAT0000760, SEQ ID NO:164) , or a complement thereof.

Mature mmu-miR-292-3p sequences include mmu-miR-292-3p, AAGUGCCGCCAGGUUUUGAGUGU, (MIMAT0000370, SEQ ID NO:165); hsa-miR-371, GUGCCGCCAUCUUUUGAGUGU, (MIMAT0000723, SEQ ID NO:166); hsa-miR-372, AAAGUGCUGCGACAUUUGAGCGU, (MIMAT0000724, SEQ ID NO:167); mmu-miR-290, CUCAAACUAUGGGGGCACUUUUU, (MIMAT0000366, SEQ ID NO:168); mmu-miR-291a-3p, AAAGUGCUUCCACUUUGUGUGCC, (MIMAT0000368, SEQ ID NO:169); mmu-miR-291a-5p, CAUCAAAGUGGAGGCCCUCUCU, (MIMAT0000367, SEQ ID NO:170); mmu-miR-291b-3p, AAAGUGCAUCCAUUUUGUUUGUC, (MIMAT0003190, SEQ ID NO:171); mmu-miR-291b-5p, GAUCAAAGUGGAGGCCCUCUC, (MIMAT0003189, SEQ ID NO:172); mmu-miR-292-5p, ACUCAAACUGGGGGCUCUUUUG, (MIMAT0000369, SEQ ID NO:173); mmu-miR-293, AGUGCCGCAGAGUUUGUAGUGU, (MIMAT0000371, SEQ ID NO:174); mmu-miR-294, AAAGUGCUUCCCUUUUGUGUGU, (MIMAT0000372, SEQ ID NO:175); mmu-miR-295, AAAGUGCUACUACUUUUGAGUCU, (MIMAT0000373, SEQ ID NO:176); rno-miR-290, CUCAAACUAUGGGGGCACUUUUU, (MIMAT0000893, SEQ ID NO:177); rno-miR-291-3p, AAAGUGCUUCCACUUUGUGUGCC, (MIMAT0000895, SEQ ID NO:178); rno-miR-291-5p, CAUCAAAGUGGAGGCCCUCUCU, (MIMAT0000894, SEQ ID NO:179); rno-miR-292-3p, AAGUGCCGCCAGGUUUUGAGUGU, (MIMAT0000897, SEQ ID NO:180); or rno-miR-292-5p, ACUCAAACUGGGGGCUCUUUUG, (MIMAT0000896, SEQ ID NO:181) , or a complement thereof.

In certain aspects, a subset of these miRNAs will be used that include some but not all of the listed miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p family members.

In one aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p sequences have a consensus sequence that can be determined by alignment of all miR family members or the alignment of miR family members from one or more species of origin. In certain embodiments one or more miR family member may be excluded from a claimed subset of miR family members.

The term miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p includes all members of the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or complements thereof. The mature sequences of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p family includes hsa-miR-15a, hsa-miR-26a, hsa-miR-31, hsa-miR-145, hsa-miR-147, hsa-miR-188, hsa-miR-215, hsa-miR-216, hsa-miR-331, or mmu-miR-292-3p.

Stem-loop sequences of miR-15, family members include hsa-mir-15a, CUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGU GCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0000069, SEQ ID NO:182); hsa-mir-15b, UUGAGGCCUUAAAGUACUGUAGCAGCACAUCAUGGUUU ACAUGCUACAGUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUU AAGGAAAUUCAU (MI0000438, SEQ ID NO:183); hsa-mir-16-1, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCGUUAAGAUUCUAAA AUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGUUGAC (MI0000070, SEQ ID NO:184); hsa-mir-16-2, GUUCCACUCUAGCAGCACGUAAAUAUUGGCGU AGUGAAAUAUAUAUUAAACACCAAUAUUACUGUGCUGCUUUAGUGUGA C (MI0000115, SEQ ID NO:185); hsa-mir-195, AGCUUCCCUGGCU CUAGCAGCACAGAAAUAUUGGCACAGGGAAGCGAGUCUGCCAAUAUUG GCUGUGCUGCUCCAGGCAGGGUGGUG (MI0000489, SEQ ID NO:186); age-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGG UGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0002945, SEQ ID NO:187); age-mir-15b, UUGAGGCCUUAAAGUACUGUAGCAGCACAUCAUGG UUUACAUACUACAGUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAA UUUAAGGAAAUUCAU (MI0002492, SEQ ID NO:188); age-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCGUUAAGAUUCUAAA AUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGUUGAC (MI0002946, SEQ ID NO:189); bta-mir-15a, CCUUGGAGUAAAGUAGCAGCACAU

AAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCA AAAAUACAAGG (MI0005458, SEQ ID NO:190); bta-mir-15b, UUGAGACCUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUACUACA GUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUC AU (MI0005012, SEQ ID NO:191); bta-mir-195, AGCUCCCC UGGCUCUAGCAGCACAGAAAUAUUGGCACUGGGAAGAAAGCCUGCCAA UAUUGGCUGUGCUGCUCCAGGCAGGGUGGUG (MI0005459, SEQ ID NO:192); dre-mir-15a-1, CCUGUCGGUACUGUAGCAGCACAGAAUGGUUUGUGAGUUAUAA CGGGGGUGCAGGCCGUACUGUGCUGCGGCAACAACGACAGG (MI0001891, SEQ ID NO:193); dre-mir-15a-2, GCCGAGGCUCUCUAGGUGAUGGUGUAG CAGCACAGAAUGGUUUGUGGUGAUACAGAGAUGCAGGCCAUGAUGUGC UGCAGCAUCAAUUCCUGGGACCUACGC (MI0001892, SEQ ID NO:194); dre-mir-15b, GUCUGUCGUCAUCUUUUUAUUUAGCCCUGAGUGCCCUGUAGCAGCACA UCAUGGUUUGUAAGUUAUAAGGGCAAAUUCCGAAUCAUGAUGUGCUGU CACUGGGAGCCUGGGAGUUUCUCCAUUAACAUGACAGC (MI0001893, SEQ ID NO:195); dre-mir-15c, CCUUAGACCGCUAAAGCAGCGCGUCAUGGUUUUC AACAUUAGAGAAGGUGCAAGCCAUCAUUUGCUGCUCUAGAGUUUUAAG G (MI0004779, SEQ ID NO:196); dre-mir-16a, CCUUCCUCGCUU UAGCAGCACGUAAAUAUUGGUGUGUUAUAGUCAAGGCCAACCCCAAUA UUAUGUGUGCUGCUUCAGUAAGGCAGG (MI0001894, SEQ ID NO:197); dre-mir-16b, CCUGAACUUGGCCGUGUGACAGACUGGCUGCCUGGCUGUAGCAGC ACGUAAAUAUUGGAGUCAAAGCACUUGCGAAUCCUCCAGUAUUGACCG UGCUGCUGGAGUUAGGCGGGCCGUUUACCGUCUGCGGGGGCCUCGGG (MI0001895, SEQ ID NO:198); dre-mir-16c, GAGGUUG UGUGUGUGUGCGUGUGUUGUCUUGCUUUAGCAGCAUGUAAAUAUUGGA GUUACUCCUUGGCCAAUGCCUCCAAUAUUGCUCGUGCUGCUGAAGCAAG AAGUCACCAAGCAGCACAUGCACGUCAUCCUU (MI0001896, SEQ ID NO:199); dre-mir-457a, UGCCUGACAGAAGCAGCACAUCAAUAUUGGCAGCUGCCCUCUCUC UGGGUUGCCAGUAUGGUUUGUGCUGCUCCCGUCAGACA (MI0002177,

SEQ ID NO:200); dre-mir-457b, GAAUGUACUAAAGCAGCACAUAAAUACUGGAGG UGAUUGUGGUGUUAUCCAGUAUUGCUGUUCUGCUGUAGUAAGACC (MI0002178, SEQ ID NO:201); fru-mir-15a, CUGGUGAUGCUGUA GCAGCACGGAAUGGUUUGUGGGUUACACUGAGAUACAGGCCAUACUGU GCUGCCGCA (MI0003469, SEQ ID NO:202); fru-mir-15b, UGAGUCCCUUAGACUGCUAUAGCAGCGCAUCAUGGUUUGUAACGAUGU AGAAAAGGGUGCAAGCCAUAAUCUGCUGCUUUAGAAUUUUAAGGAAA (MI0003447, SEQ ID NO:203); fru-mir-16, GCCACUG UGCUGUAGCAGCACGUAAAUAUUGGAGUUAAGGCUCUCUGUGAUACCU CCAGUAUUGAUCGUGCUGCUGAAGCAAAGAUGAC (MI0003471, SEQ ID NO:204); gga-mir-15a, CCUUGGCAUAACGUAGCAGCACAUAAUGGUUUGUGGGU UUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0001186, SEQ ID NO:205); gga-mir-15b, UGAGGCCUU AAAGUACUCUAGCAGCACAUCAUGGUUUGCAUGCUGUAGUGAAGAUGC GAAUCAUUAUUUGCUGCUUUAGAAAUUUAAGGAA (MI0001223, SEQ ID NO:206); gga-mir-16-1, GUCUGUCAUACUCUAGCAGCACGUAAAUAUUGGUGUUA AAACUGUAAAUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGCU (MI0001185, SEQ ID NO:207); gga-mir-16-2, CCUACUUGUU CCGCCCUAGCAGCACGUAAAUAUUGGUGUAGUAAAAUAAACCUUAAAC CCCAAUAUUAUUGUGCUGCUUAAGCGUGGCAGAGAU (MI0001222, SEQ ID NO:208); ggo-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUG GAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0002947, SEQ ID NO:209); ggo-mir-15b, UUGAGGC CUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUGCUACAGUCAAGA UGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUCAU (MI0002491, SEQ ID NO:210); ggo-mir-16, GUCAGCAGUGCCUUAGCAGCA CGUAAAUAUUGGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGU GCUGCUGAAGUAAGGUUGAC (MI0002948, SEQ ID NO:211); bta-mir-16, CAUACUUGUUCCGCUGUAGCAGCACGUAAAUAUUGGCGUAGUAAAAUA AAUAUUAAACACCAAUAUUAUUGUGCUGCUUUAGCGUGACAGGGA (MI0004739, SEQ ID NO:212); ggo-mir-195,

AGCUUCCUGGGCUCUAGCAGCACAGAAAUAUUGGCACAGGGAAGCGAG UCUGCCAAUAUUGGCUGUGCUGCUCCAGGCAGGGUGGUG (MI0002617, SEQ ID NO:213); lca-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUG GUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAA UACAAGG (MI0002955, SEQ ID NO:214); lca-mir-16, GUCAGCAGUGC CUUAGCAGCACGUAAAUAUUGGUGUUAAGAUUCUAAAAUUAUCUCUAA GUAUUAACUGUGCCG (MI0002956, SEQ ID NO:215); lla-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGG UGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0002963, SEQ ID NO:216); lla-mir-15b, UUGAGGCCUUAAAGUACUGUAGCAGCACAU CAUGGUUUACAUACUACAGUCAAGAUGCGAAUCAUUAUUUGCUGCUCU AGAAAUUUAAGGAAAUUCAU (MI0002497, SEQ ID NO:217); lla-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCGCUAAGAUUCUAAA AUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGUUGGC (MI0002964, SEQ ID NO:218); mdo-mir-15a, CCUUGGGGUAAAGUAGCAGCACAUA AUGGUUUGUUGGUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAA AAAUACAAGG (MI0005333, SEQ ID NO:219); mdo-mir-16, GUCAACAG UGCCUUAGCAGCACGUAAAUAUUGGCGUUAAGAUUUUAAAAGUAUCUC CAGUAUUAACUGUGCUGCUGAAGUAAGGUUGGCC (MI0005334, SEQ ID NO:220); mml-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAU UUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUACAAGG (MI0002957, SEQ ID NO:221); mml-mir-15b, UUGAGGCCUUAAA GUACUGUAGCAGCACAUCAUGGUUUACAUACUACAGUCAAGAUGCGAA UCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUCAU (MI0002496, SEQ ID NO:222); mml-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCG UUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAG GUUGAC (MI0002958, SEQ ID NO:223); mmu-mir-15a, CCCUUGGAGUAAAGUAGCAGCACAUAAUGGUUUGUGGAUGUUGAAAAG GUGCAGGCCAUACUGUGCUGCCUCAAAAUACAAGGA (MI0000564, SEQ ID NO:224); mmu-mir-15b, CUGUAGCAGCACAUCAUGGUUUACAUACUAC AGUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAG (MI0000140, SEQ ID

NO:225); mmu-mir-16-1, AUGUCAGCGGUGCCUUAGCAGCACG UAAAUAUUGGCGUUAAGAUUCUGAAAUUACCUCCAGUAUUGACUGUGC UGCUGAAGUAAGGUUGGCAA (MI0000565, SEQ ID NO:226); mmu-mir-16-2, CAUGCUUGUUCCACUCUAGCAGCACGUAAAUAUUGGCGUAGUGAAAUA AAUAUUAAACACCAAUAUUAUUGUGCUGCUUUAGUGUGACAGGGAUA (MI0000566, SEQ ID NO:227); mmu-mir-195, ACACCCAACUC UCCUGGCUCUAGCAGCACAGAAAUAUUGGCAUGGGGAAGUGAGUCUGC CAAUAUUGGCUGUGCUGCUCCAGGCAGGGUGGUGA (MI0000237, SEQ ID NO:228); mne-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUG GUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAA UACAAGG (MI0002949, SEQ ID NO:229); mne-mir-15b, UUGAGGCCU UAAAGUACUGUAGCAGCACAUCAUGGUUUACAUACUACAGUCAAGAUG CGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUCAU (MI0002498, SEQ ID NO:230); mne-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAA UAUUGGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUGCUGCU GAAGUAAGGUUGAC (MI0002950, SEQ ID NO:231); ppa-mir-15a, CCUUGGAGU AAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCA UAUUGUGCUGCCUCAAAAAUACAAGG (MI0002953, SEQ ID NO:232); ppa-mir-15b, UUGAGGCCUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUGCUACA GUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUC AU (MI0002493, SEQ ID NO:233); ppa-mir-16, GUCAGCAGUGCCUUAGCAGCAC GUAAAUAUUGGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUG CUGCUGAAGUAAGGUUGAC (MI0002954, SEQ ID NO:234); ppa-mir-195, AGCUUCCCUGGCUCUAGCAGCACAGAAAUAUUGGCACAGGGAAGCGAG UCUGCCAAUAUUGGCUGUGCUGCUCCAGGCAGGGUGGUG (MI0002618, SEQ ID NO:235); ppy-mir-15a, CCUUGGAGUAAAGUAGCAGCACAUAAUGGUUU GUGGAUUUUGAAAAGGUGCAGGCCAUAUUGUGCUGCCUCAAAAAUACA AGG (MI0002959, SEQ ID NO:236); ppy-mir-15b, UUGAGGCCUUAAAGU ACUGUAGCAGCACAUCAUGGUUUACAUGCUACAGUCAAGAUGCGAAUC

AUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUCAU (MI0002494, SEQ ID NO:237); ppy-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCG UUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAG GUUGAC (MI0002960, SEQ ID NO:238); ptr-mir-15a, CCUUGGAGU AAAGUAGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCA UAUUGUGCUGCCUCAAAAAUACAAGG (MI0002961, SEQ ID NO:239); ptr-mir-15b,
UUGAGGCCUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUGCUACA GUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUC AU (MI0002495, SEQ ID NO:240); ptr-mir-16, GUCAGCAGUGCCUUAGCAGCAC
GUAAAUAUUGGCGUUAAGAUUCUAAAAUUAUCUCCAGUAUUAACUGUG CUGCUGAAGUAAGGUUGAC (MI0002962, SEQ ID NO:241); rno-mir-15b, UUGGAACCUUAAAGUACUGUAGCAGCACAUCAUGGUUUACAUACUACA GUCAAGAUGCGAAUCAUUAUUUGCUGCUCUAGAAAUUUAAGGAAAUUC AU (MI0000843, SEQ ID NO:242); rno-mir-16, CAUACUUGUUCC GCUCUAGCAGCACGUAAAUAUUGGCGUAGUGAAAUAAAUAUUAAACAC CAAUAUUAUUGUGCUGCUUUAGUGUGACAGGGAUA (MI0000844, SEQ ID NO:243); rno-mir-195, AACUCUCCUGGCUCUAGCAGCACAGAAAUAUU GGCACGGGUAAGUGAGUCUGCCAAUAUUGGCUGUGCUGCUCCAGGCAG GGUGGUG (MI0000939, SEQ ID NO:244); sla-mir-15a, CCUUGGAGUAAAGU AGCAGCACAUAAUGGUUUGUGGAUUUUGAAAAGGUGCAGGCCAUAUUG UGCUGCCUCAAAAAUACAAGG (MI0002951, SEQ ID NO:245); sla-mir-16, GUCAGCAGUGCCUUAGCAGCACGUAAAUAUUGGCGUUAAGAUUCUAAA AUUAUCUCCAGUAUUAACUGUGCUGCUGAAGUAAGGUUGAC
(MI0002952, SEQ ID NO:246); ssc-mir-15b, UUGAGGCCUUAAAGUACUGCCGCAG
CACAUCAUGGUUUACAUACUACAAUCAAGAUGCGAAUCAUUAUUUGCU GCUCUAGAAAUUUAAGGAAAUUCAU (MI0002419, SEQ ID NO:247); tni-mir-15a,
CUGGUGAUGCUGUAGCAGCACGGAAUGGUUUGUGAGUUACACUGAGAU ACAAGCCAUGCUGUGCUGCCGCA (MI0003470, SEQ ID NO:248); tni-mir-15b, GCCCUUAGACUGCUUUAGCAGCGCAUCAUGGUUUGUAAUGAUGUGGAA AAAAGGUGCAAACCAUAAUUUGCUGCUUUAGAAUUUUAAGGAA

(MI0003448, SEQ ID NO:249); tni-mir-16, UAGCAGCACGUAAAUAUUGGAGUU AAGGCUCUCUGUGAUACCUCCAGUAUUGAUCGUGCUGCUGAAGCAAAG (MI0003472, SEQ ID NO:250); xtr-mir-15a, CCUUGACGUAAAGUAGCAGCACAUA AUGGUUUGUGGGUUACACAGAGGUGCAGGCCAUACUGUGCUGCCGCCA AAACACAAGG (MI0004799, SEQ ID NO:251); xtr-mir-15b, UGUCCUAAAGAAGUGUAGCAGCACAUCAUGAUUUGCAUGCUGUAUUAU AGAUUCUAAUCAUUUUUUGCUGCUUCAUGAUAUUGGGAAA (MI0004800, SEQ ID NO:252); xtr-mir-15c, CUUUGAGGUGAUCUAGCAGCACAUCAUG GUUUGUAGAAACAAGGAGAUACAGACCAUUCUGAGCUGCCUCUUGA, MI0004892 (SEQ ID NO:253); xtr-mir-16a, GCCAGCAGUCCUUUAGCAGCACG UAAAUAUUGGUGUUAAAAUGGUCCCAAUAUUAACUGUGCUGCUAGAGU AAGGUUGGCCU (MI0004802, SEQ ID NO:254); xtr-mir-16b, AAUUGCUCCGCAUUAGCAGCACGUAAAUAUUGGGUGAUAUGAUAUGGA GCCCCAGUAUUAUUGUACUGCUUAAGUGUGGCAAGG (MI0004910, SEQ ID NO:255); and xtr-mir-16c, UUUAGCAGCACGUAAAUACUGGAGU UCAUGACCAUAUCUGCACUCUCCAGUAUUACUUUGCUGCUAUAUU (MI0004801, SEQ ID NO:256) or complements thereof.

Stem-loop sequences of miR-26, family members include, hsa-mir-26a-1, GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCCAAUGGG CCUAUUCUUGGUUACUUGCACGGGGACGC (MI0000083, SEQ ID NO:257); hsa-mir-26a-2, GGCUGUGGCUGGAUUCAAGUAAUCCAGGAUAGGCUGUUUCCAU CUGUGAGGCCUAUUCUUGAUUACUUGUUUCUGGAGGCAGCU (MI0000750, SEQ ID NO:258);hsa-mir-26b, CCGGGACCCAGUUCAAGUAAUUCAGGAUA GGUUGUGUGCUGUCCAGCCUGUUCUCCAUUACUUGGCUCGGGGACCGG (MI0000084, SEQ ID NO:259); bta-mir-26a, GGCUGUGGCUGGAUU CAAGUAAUCCAGGAUAGGCUGUUUCCAUCUGUGAGGCCUAUUCUUGAU UACUUGUUUCUGGAGGCAGCU (MI0004731, SEQ ID NO:260); bta-mir-26b, UGCCCGGGACCCAGUUCAAGUAAUUCAGGAUAGGUUGUGUGCUGUCCA GCCUGUUCUCCAUUACUUGGCUCGGGGGCCGGUGCCC (MI0004745, SEQ

ID NO:261); dre-mir-26a-1, UUUGGCCUGGUUCAAGUAAUCCAGGAUAGGCU UGUGAUGUCCGGAAAGCCUAUUCGGGAUGACUUGGUUCAGGAAUGA (MI0001923, SEQ ID NO:262); dre-mir-26a-2, GUGUGGACUUGAGUGCUGG AAGUGGUUGUUCCCUUGUUCAAGUAAUCCAGGAUAGGCUGUCUGUCCU GGAGGCCUAUUCAUGAUUACUUGCACUAGGUGGCAGCCGUUGCCCUUC AUGGAACUCAUGC (MI0001925, SEQ ID NO:263); dre-mir-26a-3, CUAAGCUGAU ACUGAGUCAGUGUGUGGCUGCAACCUGGUUCAAGUAAUCCAGGAUAGG CUUUGUGGACUAGGGUUGGCCUGUUCUUGGUUACUUGCACUGGGUUGC AGCUACUAAACAACUAAGAAGAUCAGAAGAG (MI0001926, SEQ ID NO:264); fru-mir-26, AGGCCUCGGCCUGGUUCAAGUAAUCCAGGAUAGGCUGGUUAACCCU GCACGGCCUAUUCUUGAUUACUUGUGUCAGGAAGUGGCCGUG (MI0003369, SEQ ID NO:265); gga-mir-26a, GUCACCUGGUUCAAGUAA UCCAGGAUAGGCUGUAUCCAUUCCUGCUGGCCUAUUCUUGGUUACUUG CACUGGGAGGC (MI0001187, SEQ ID NO:266); ggo-mir-26a, GUGGCCUCGUUCA AGUAAUCCAGGAUAGGCUGUGCAGGUCCCAAUGGGCCUAUUCUUGGUU ACUUGCACGGGGACGC (MI0002642, SEQ ID NO:267); lla-mir-26a, GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCCAAUGGG CCUAUUCUUGGUUACUUGCACGGGGACGC (MI0002644, SEQ ID NO:268); mml-mir-26a, GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCC AAUGGGCCUAUUCUUGGUUACUUGCACGGGGACGC (MI0002646, SEQ ID NO:269); mmu-mir-26a-1, AAGGCCGUGGCCUCGUUCAAGUAAUCCAGG AUAGGCUGUGCAGGUCCCAAGGGGCCUAUUCUUGGUUACUUGCACGGG GACGCGGGCCUG (MI0000573, SEQ ID NO:270); mmu-mir-26a-2, GGCUGCGGCUGGAUUCAAGUAAUCCAGGAUAGGCUGUGUCCGUCCAUG AGGCCUGUUCUUGAUUACUUGUUUCUGGAGGCAGCG (MI0000706, SEQ ID NO:271); mmu-mir-26b, UGCCCGGGACCCAGUUCAAGUAAUUCAGGAUAGGUU GUGGUGCUGACCAGCCUGUUCUCCAUUACUUGGCUCGGGGGCCGGUGCC (MI0000575, SEQ ID NO:272); mne-mir-26a, GUGGCCUCG UUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCCAAUGGGCCUAUUCUU

GAUUACUUGCACGGGGACGC (MI0002645, SEQ ID NO:273); ppa-mir-26a, GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCCAAUGGG CCUAUUCUUGGUUACUUGCACGGGGACGC (MI0002647, SEQ ID NO:274); ptr-mir-26a, GUGGCCUCGUUCAAGUAAUCCAGGAUAGGCUGUGCAGGUCCCAA UGGGCCUAUUCUUGGUUACUUGCACGGGGACGC (MI0002641, SEQ ID NO:275); rno-mir-26a, AAGGCCGUGGCCUUGUUCAAGUAAUCCAGG AUAGGCUGUGCAGGUCCCAAGGGGCCUAUUCUUGGUUACUUGCACGGG GACGCGGGCCUG (MI0000857, SEQ ID NO:276); rno-mir-26b, UGCCCGGGACCCAGUUCAAGUAAUUCAGGAUAGGUUGUGGUGCUGGCC AGCCUGUUCUCCAUUACUUGGCUCGGGGGCCGGUGCC (MI0000858, SEQ ID NO:277); ssc-mir-26a, GGCUGUGGCUGGAUUCAAGUAAUCCAGGAUAG GCUGUUUCCAUCUGUGAGGCCUAUUCUUGAUUACUUGUUUCUGGAGGC AGCU (MI0002429, SEQ ID NO:278); tni-mir-26, GCGUUAG GCCUCGGCCUGGUUCAAGUAAUCCAGGAUAGGCUGGUUAACCCUGCACG GCCUAUUCUUGAUUACUUGUGUCAGGAAGUGGCCGCCAGC (MI0003370, SEQ ID NO:279); xtr-mir-26-1, GGCUGCUGCCUGGUUCAAGUAAUCCAGG AUAGGCUGUUUCCUCAAAGCACGGCCUACUCUUGAUUACUUGUUUCAG GAAGUAGCU (MI0004807, SEQ ID NO:280); xtr-mir-26-2, UGGGCGCUCGCUUCAAGU, MI0004808, SEQ ID NO:281) or complement thereof.

Stem-loop sequences of miR-31, family members include Hsa-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGGGAACCUGCUA UGCCAACAUAUUGCCAUCUUUCC (MI0000089, SEQ ID NO:282); Ame-mir-31a, AUCACGAUUCUAACUGGGCGCCUCGAAGGCAAGAUGUCGGCAUAGCUG AUGCGAUUUUAAAAUUCGGCUGUGUCACAUCCAGCCAACCGAACGCUCA GAC (MI0005737, SEQ ID NO:283); Bmo-mir-31, GUCGAGCCGGU GGCUGGGAAGGCAAGAAGUCGGCAUAGCUGUUUGAAUAAGAUACACGG CUGUGUCACUUCGAGCCAGCUCAAUCCGCCGGCUUUCUUCAAUUUCAAG AUUUGCGGAUGCU (MI0005377, SEQ ID NO:284); Bta-mir-31, UCCUGUAA CUUGGAACUGGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGCG AACCUGCUAUGCCAACAUAUUGCCAUCUCUCUUGUCCG (MI0004762, SEQ

ID NO:285); Dme-mir-31a, UCCGUUGGUAAAUUGGCAAGAUGUCGGCAUAGCUGA CGUUGAAAAGCGAUUUUGAAGAGCGCUAUGCUGCAUCUAGUCAGUUGU UCAAUGGA (MI0000420, SEQ ID NO:286); Dme-mir-31b, CAAAUAAU GAAUUUGGCAAGAUGUCGGAAUAGCUGAGAGCACAGCGGAUCGAACAU UUUAUCGUCCGAAAAAAUGUGAUUAUUUUUGAAAAGCGGCUAUGCCUC AUCUAGUCAAUUGCAUUACUUUG (MI0000410, SEQ ID NO:287); Dps-mir-31a, UCUGUUGGUAAAUUGGCAAGAUGUCGGCAUAGCUGAAGUUGAAAAGCG AUCUUUGAGAACGCUAUGCUGCAUCUAGUCAGUUAUUCAAUGGA (MI0001314, SEQ ID NO:288); Dps-mir-31b, AAUUUGGCAAGAUGUCGGAAUAGCUGAGAGC AAAAAGAAGAUGAUUUGAAAUGCGGCUAUGCCUCAUCUAGUCAAUUGC AUUCAUUUGA (MI0001315, SEQ ID NO:289); Dre-mir-31, GAAGAGAU GGCAAGAUGUUGGCAUAGCUGUUAAUGUUUAUGGGCCUGCUAUGCCUC CAUAUUGCCAUUUCUG (MI0003691, SEQ ID NO:290); Gga-mir-31, UUCUUUCAUGCAGAGCUGGAGGGGAGGCAAGAUGUUGGCAUAGCUGUU AACCUAAAAACCUGCUAUGCCAACAUAUUGUCAUCUUUCCUGUCUG (MI0001276, SEQ ID NO:291); Ggo-mir-31, GGAGAGGAGGCAAGAUG CUGGCAUAGCUGUUGAACUGGGAACCUGCUAUGCCAACAUAUUGCCAU CUUUCC (MI0002673, SEQ ID NO:292); Mdo-mir-31, AGCUGGAGAGGAGGCAAGAUGUUGGCAUAGCUGUUGAACUGAGAACCU GCUAUGCCAACAUAUUGCCAUCUUUCUUGUCUAUCAGCA (MI0005278, SEQ ID NO:293); mml-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGA ACUGGGAACCUGCUAUGCCAACAUAUUGCCAUCUUUCC (MI0002671, SEQ ID NO:294); Mmu-mir-31, UGCUCCUGUAACUCGGAACUGGAGAGGAGGCAAGA UGCUGGCAUAGCUGUUGAACUGAGAACCUGCUAUGCCAACAUAUUGCC AUCUUUCCUGUCUGACAGCAGCU (MI0000579, SEQ ID NO:295); Mne-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGGGAACCUGCUA UGCCAACAUAUUGCCAUCUUUCC (MI0002675, SEQ ID NO:296); ppa-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGGGAACCUGCUA

UGCCAACAUAUUGCCAUCUUUCC (MI0002676, SEQ ID NO:297); ppy-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGGGAACCUGCUA UGCCAACAUAUUGCCAUCUUUCC (MI0002674, SEQ ID NO:298); ptr-mir-31, GGAGAGGAGGCAAGAUGCUGGCAUAGCUGUUGAACUGGGAACCUGCUA UGCCAACAUAUUGCCAUCUUUCC (MI0002672, SEQ ID NO:299); rno-mir-31, UGCUCCUGAAACUUGGAACUGGAGAGGAGGCAAGAUGCUGGCAUAGCU GUUGAACUGAGAACCUGCUAUGCCAACAUAUUGCCAUCUUUCCUGUCU GACAGCAGCU (MI0000872, SEQ ID NO:300); sme-mir-31b, AUUGAUAA UGACAAGGCAAGAUGCUGGCAUAGCUGAUAAACUAUUUAUUACCAGCU AUUCAGGAUCUUUCCCUGAAUAUAUCAAU (MI0005146, SEQ ID NO:301); xtr-mir-31,
CCUAGUUCUAGAGAGGAGGCAAGAUGUUGGCAUAGCUGUUGCAU CUGAAACCAGUUGUGCCAACCUAUUGCCAUCUUUCUUGUCUACC (MI0004921, SEQ ID NO:302) or complement thereof.

Stem-loop sequences of miR-145, family members include hsa-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCUUAGAUGCUAAG AUGGGGAUUCCUGGAAAUACUGUUCUUGAGGUCAUGGUU (MI0000461, SEQ ID NO:303); bta-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCU UAGAUGCUAAGAUGGGGAUUCCUGGAAAUACUGUUCUUGAGGUCAUGG UU (MI0004756, SEQ ID NO:304); dre-mir-145, UCAGUCUUCAUCAU UUCCUCAUCCCCGGGGUCCAGUUUUCCCAGGAAUCCCUUGGGCAAUCGA AAGGGGGAUUCCUGGAAAUACUGUUCUUGGGGUUGGGGGUGGACUACU GA (MI0002010, SEQ ID NO:305); ggo-mir-145, CACCUUGUCCUCACG GUCCAGUUUUCCCAGGAAUCCCUUAGAUGCUAAGAUGGGGAUUCCUGG AAAUACUGUUCUUGAGGUCAUGGUU (MI0002560, SEQ ID NO:306); mdo-mir-145,
CUCAGGGUCCAGUUUUCCCAGGAAUCCCUUAGAUGCUAAGAUGGGGAU UCCUGGAAAUACUGUUCUUGAG (MI0005305, SEQ ID NO:307); mml-mir-145,
CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCUUAAAUGCUAAG AUGGGGAUUCCUGGAAAUACUGUUCUUGAGGUCAUGGUU (MI0002558, SEQ ID NO:308); mmu-mir-145, CUCACGGUCCAGUUUUCCCAGGAAUCCCU

UGGAUGCUAAGAUGGGGAUUCCUGGAAAUACUGUUCUUGAG (MI0000169, SEQ ID NO:309); mne-mir-145, CACCUUGUCCUCACGGUCCAGU UUUCCCAGGAAUCCCUUAAAUGCUAAGAUGGGGAUUCCUGGAAAUACU GUUCUUGAGGUCAUGGUU (MI0002562, SEQ ID NO:310); ppy-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCUUAGAUGCUAAG AUGGGGAUUCCUGGAAAUACUGUUCUUGAGGUCAUGGUU (MI0002561, SEQ ID NO:311); ptr-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCA GGAAUCCCUUAGAUGCUAAGAUGGGGAUUCCUGGAAAUACUGUUCUUG AGGUCAUGGUU (MI0002559, SEQ ID NO:312); rno-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCUUGGAUGCUAAG AUGGGGAUUCCUGGAAAUACUGUUCUUGAGGUCAUGGCU (MI0000918, SEQ ID NO:313); ssc-mir-145, CACCUUGUCCUCACGGUCCAGUUUUCCCAGGAAUCCCU UAGAUGCUGAGAUGGGGAUUCCUGUAAAUACUGUUCUUGAGGUCAUGG (MI0002417, SEQ ID NO:314); xtr-mir-145, ACCUAUUCCUCA AGGUCCAGUUUUCCCAGGAAUCCCUUGGGUGCUGUGGUGGGGAUUCCU GGAAAUACUGUUCUUGGGGUGUAGGC (MI0004939, SEQ ID NO:315) or complements thereof.

Stem-loop sequences of miR-147, family members include hsa-mir-147, AAUCUAAAGACAACAUUUCUGCACACACACCAGACUAUGGAAGCCAGU GUGUGGAAAUGCUUCUGCUAGAUU (MI0000262, SEQ ID NO:316); gga-mir-147-1, AAUCUAGUGGAAUCACUUCUGCACAAACUUGACUACUGAAAUCAGUGU GCGGAAAUGCUUCUGCUACAUU (MI0003696, SEQ ID NO:317); gga-mir-147-2, AAUCUAGUGGAAUCACUUCUGCACAAACUUGACUACUGAAAUCAGUGU GCGGAAAUGCUUCUGCUACAUU (MI0003697, SEQ ID NO:318); mne-mir-147, AAUCUAAAGAAAACAUUUCUGCACACACACCAGACUAUUGAAGCCAGU GUGUGGAAAUGCUUCUGCUACAUU (MI0002773, SEQ ID NO:319); ppa-mir-147, AAUCUAAAGAAAACAUUUCUGCACACACACCAGACUAUGGAAGCCAGU GUGUGGAAAUGCUUCUGCUAGAUU (MI0002774, SEQ ID NO:320); ppy-mir-147,

AAUCUAAAGAAAACAUUUCUGCACACACACCAGACUAUGGAAGCCAGU GUGUGGAAAUGCUUCUGCUAGAUU (MI0002771, SEQ ID NO:321); ptr-mir-147, AAUCUAAAGAAAACAUUUCUGCACACACACCAGACUAUGGAAGCCAGU GUGUGGAAAUGCUUCUGCUAGAUU (MI0002770, SEQ ID NO:322); sla-mir-147, AAUCUAAAGAAAACAUUUCUGCACACACACCAGACUAUUGAAGCCAGU GUGUGGAAAUGCUUCUGCCACAUU (MI0002772, SEQ ID NO:323) or a complement thereof.

Stem-loop sequences of miR-188, family members include hsa-mir-188, UGCUCCCUCUCUCACAUCCCUUGCAUGGUGGAGGGUGAGCUUUCUGAAA ACCCCUCCCACAUGCAGGGUUUGCAGGAUGGCGAGCC (MI0000484, SEQ ID NO:324); hsa-mir-532, CGACUUGCUUUCUCUCCUCCAUGCCUUGAGUGUAGG ACCGUUGGCAUCUUAAUUACCCUCCCACACCCAAGGCUUGCAAAAAAGC GAGCCU (MI0003205, SEQ ID NO:325); hsa-mir-660, CUGCUCCUUCUCCCAUACCCAUUGCAUAUCGGAGUUGUGAAUUCUCAAA ACACCUCCUGUGUGCAUGGAUUACAGGAGGGUGAGCCUUGUCAUCGUG (MI0003684, SEQ ID NO:326); bta-mir-532, GACUUGCUUUCUCUCU UACAUGCCUUGAGUGUAGGACCGUUGGCAUCUUAAUUACCCUCCCACAC CCAAGGCUUGCAGGAGAGCCA (MI0005061, SEQ ID NO:327); bta-mir-660, CUGCUCCUUCUCCCGUACCCAUUGCAUAUCGGAGCUGUGAAUUCUCAAA GCACCUCCUAUGUGCAUGGAUUACAGGAGGG (MI0005468, SEQ ID NO:328); mml-mir-188, UGCUCCCUCUCUCACAUCCCUUGCAUGGUGGAGGGUGAG CUUUAUGAAAACCCCUCCCACAUGCAGGGUUUGCAGGAUGGUGAGCC (MI0002608, SEQ ID NO:329); mmu-mir-188, UCUCACAUCCCUUGCAUGGUGGAGGGUGAGCUCUCUGAAAACCCCUCCC ACAUGCAGGGUUUGCAGGA (MI0000230, SEQ ID NO:330); mmu-mir-532, CAGAUUUGCUUUUUCUCUUCCAUGCCUUGAGUGUAGGACCGUUGACAU CUUAAUUACCCUCCCACACCCAAGGCUUGCAGGAGAGCAAGCCUUCUC (MI0003206, SEQ ID NO:331); mne-mir-188, UGCUCCCUCUCU CACAUCCCUUGCAUGGUGGAGGGUGAGCUUUAUGAAAACCCCUCCCACA

UGCAGGGUUUGCAGGAUGGUGAGCC (MI0002611, SEQ ID NO:332); ppa-mir-188, UGCUCCCUCUCUCACAUCCCUUGCAUGGUGGAGGGUGAGCUUUCUGAAA ACCCCUCCCACAUGCAGGGUUUGCAGGAUGGCGAGCC (MI0002612, SEQ ID NO:333); ppy-mir-188, UGCUCCCUCUCUCACAUCCCUUGCAUGGUGGAG GGUGAGCUUUCUGAAAACCCCUCCCACAUGCAGGGUUUGCAGGAUGGC GAGCC (MI0002610, SEQ ID NO:334); ptr-mir-188, UGCUCCCUCUCUCACA UCCCUUGCAUGGUGGAGGGUGAACUUUCUGAAAACCCCUCCCACAUGCA GGGUUUGCAGGAUGGCGAGCC (MI0002609, SEQ ID NO:335) or complements thereof.

Stem-loop sequences of miR-215, family members include hsa-mir-215, AUCAUUCAGAAAUGGUAUACAGGAAAAUGACCUAUGAAUUGACAGACA AUAUAGCUGAGUUUGUCUGUCAUUUCUUUAGGCCAAUAUUCUGUAUGA CUGUGCUACUUCAA (MI0000291, SEQ ID NO:336); hsa-mir-192, GCCGAGA CCGAGUGCACAGGGCUCUGACCUAUGAAUUGACAGCCAGUGCUCUCGUC UCCCCUCUGGCUGCCAAUUCCAUAGGUCACAGGUAUGUUCGCCUCAAUG CCAGC (MI0000234, SEQ ID NO:337); bta-mir-192, AGACCGAGUGCACAG GGCUCUGACCUAUGAAUUGACAGCCAGUGCUCUUGUGUCCCCUCUGGCU GCCAAUUCCAUAGGUCACAGGUAUGUUCGCCUCAAUGCCAGC (MI0005035, SEQ ID NO:338); bta-mir-215, UGUACAGGAAAAUGACCUAUGAAUUGACAG ACAACGUGACUAAGUCUGUCUGUCAUUUCUGUAGGCCAAUGUUCUGUA U (MI0005016, SEQ ID NO:339); dre-mir-192, CUAGGACACAGGGU GAUGACCUAUGAAUUGACAGCCAGUGUUUGCAGUCCAGCUGCCUGUCA GUUCUGUAGGCCACUGCCCUGUU (MI0001371, SEQ ID NO:340); fru-mir-192, UGGGACGUGAGGUGAUGACCUAUGAAUUGACAGCCAGUAACUGGAGCC UCUGCCUGUCAGUUCUGUAGGCCACUGCUACGUU (MI0003257, SEQ ID NO:341); gga-mir-215, UCAGUAAGAACUGGUGUCCAGGAAAAUGACCUAUGAAUUGA CAGACUGCUUUCAAAAUGUGCCUGUCAUUUCUAUAGGCCAAUAUUCUG UGCACUUUUCCUACUU (MI0001203, SEQ ID NO:342); ggo-mir-215, AUCAUUCAGAAAUGGUAUACGGGAAAAUGACCUAUGAAUUGACAGACA AUAUAGCUGAGUUUGUCUGUCAUUUCUUUAGACCAAUAUUCUGUAUGA

CUGUGCUACUUCAA (MI0003031, SEQ ID NO:343); mml-mir-215, AUCAUUAAGAAAUGGUAUACAGGAAAAUGACCUAUGAAUUGACAGACA CUAUAGCUGAGUUUGUCUGUCAUUUCUUUAGGCCAAUAUUCUGUAUGA CUGUGCUACUUCAA (MI0003025, SEQ ID NO:344); mmu-mir-192, CGUGCACAGGGCUCUGACCUAUGAAUUGACAGCCAGUACUCUUUUCUCU CCUCUGGCUGCCAAUUCCAUAGGUCACAGGUAUGUUCACC (MI0000551, SEQ ID NO:345); mmu-mir-215, AGCUCUCAGCAUCAACGGUGUACAGGAGAAUGA CCUAUGAUUUGACAGACCGUGCAGCUGUGUAUGUCUGUCAUUCUGUAG GCCAAUAUUCUGUAUGUCACUGCUACUUAAA (MI0000974, SEQ ID NO:346); mne-mir-215, AUCAUUAAGAAAUGGUAUACAGGAAAAUGACCUAUGAAUUGACA GACACUAUAGCUGAGUUUGUCUGUCAUUUCUUUAGGCCAAUAUUCUGU AUGACUGUGCUACUUCAA (MI0003033, SEQ ID NO:347); ppy-mir-215, AUCAUUCAGAAAUGGUAUACAGGAAAAUGACCUAUGAAUUGACAGACA AUACAGCUGAGUUUGUCUGUCAUUUCUUUAGGCCAAUAUUCUGUACAA CUGUGCUACUUCAA (MI0003029, SEQ ID NO:348); ptr-mir-215, AUCAUUCAGAAAUGGUAUACGGGAAAAUGACCUAUGAAUUGACAGACA AUAUAGCUGAGUUUGUCUGUCAUUUCUUUAGGCCAAUAUUCUGUAUGA CUGUGCUACUUCAA (MI0003027, SEQ ID NO:349); rno-mir-192, GUCAAGAUGGAGUGCACAGGGCUCUGACCUAUGAAUUGACAGCCAGUA CUCUGAUCUCGCCUCUGGCUGCCAGUUCCAUAGGUCACAGGUAUGUUCG CCUCAAUGCCAGC (MI0000935, SEQ ID NO:350); rno-mir-215, GGUGUACA GGACAAUGACCUAUGAUUUGACAGACAGUGUGGCUGCGUGUGUCUGUC AUUCUGUAGGCCAAUAUUCUGUAUGUCUCUCCUCCUUACAA (MI0003482, SEQ ID NO:351); tni-mir-192, CACGAGGUGAUGACCUAUGAAUUGACAGCCAGUAA CUGGAGCCUCUGCCUGUCAGUUCUGUAGGCCACUGCUGCGUCCGUCCC (MI0003258, SEQ ID NO:352); xtr-mir-192, GAGUGUACGGGCCUA UGACCUAUGAAUUGACAGCCAGUGGAUGUGAAGUCUGCCUGUCAAUUC UGUAGGCCACAGGUUCGUCCACCU (MI0004855, SEQ ID NO:353); xtr-mir-215, AACUGGUAACCAGGAGGAUGACCUAUGAAAUGACAGCCACUUCCAUAC

CAAACAUGUCUGUCAUUUCUGUAGGCCAAUAUUCUGAUUGCUUUGUUG A (MI0004868, SEQ ID NO:354) or complements thereof.

Stem-loop sequences of miR-216, family members include hsa-mir-216, GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAACUGUGAGAUGUUCA UACAAUCCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUU CCUAGCCCUCACGA (MI0000292, SEQ ID NO:355); dre-mir-216a-1, GCUGAUUUUUGGCAUAAUCUCAGCUGGCAACUGUGAGUAGUGUUUUCA UCCCUCUCACAGGCGCUGCUGGGGUUCUGUCACACACAGCA (MI0001382, SEQ ID NO:356); dre-mir-216a-2, GCUGAUUUUUGGCAUAAUCUCAGCUGGCAA CUGUGAGUAGUGUUUUCAUCCCUCUCACAGGCGCUGCUGGGGUUCUGU CACACACAGCA (MI0002047, SEQ ID NO:357); dre-mir-216b-1, ACUGACUGG GUAAUCUCUGCAGGCAACUGUGAUGUGAUUACAGUCUCACAUUGACCU GAAGAGGUUGAGCAGUCUGU (MI0002048, SEQ ID NO:358); dre-mir-216b-2, CUGACUGGGUAAUCUCUGCAGGCAACUGUGAUGUGAUUACAGUCUCAC AUUGACCUGAAGAGGUUGUGCAGUCUGU (MI0002049, SEQ ID NO:359); fru-mir-216a, UUGGUAAAAUCUCAGCUGGCAACUGUGAGUCGUUCACUAGCUGCU CUCACAAUGGCCUCUGGGAUUAUGCUAA (MI0003291, SEQ ID NO:360); fru-mir-216b, UGACUGUUUAAUCUCUGCAGGCAACUGUGAUGGUGUUUUAUAU UCUCACAAUCACCUGGAGAGAUUCUGCAGUUUAU (MI0003293, SEQ ID NO:361); gga-mir-216, GAUGGCUGUGAAUUGGCUUAAUCUCAGCUGGCAAC UGUGAGCAGUUAAUAAUUCUCACAGUGGUAUCUGGGAUUAUGCUAAAC ACAGCAAUUUCUUUGCUCUAAUG (MI0001200, SEQ ID NO:362); ggo-mir-216, GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAACUGUGAGAUGUUCA UACAAUCCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUU CCUAGCCCUCACGA (MI0002863, SEQ ID NO:363); lca-mir-216, GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAACUGUGAGAUGUUCA UACAAUCCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUU CCUAGCCCUCACGA (MI0002861, SEQ ID NO:364); mdo-mir-216, GAUGGCUGUGAAUUGGCUUAAUCUCAGCUGGCAACUGUGAGAUGUUAA

UAAAUUCCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUU C (MI0005320, SEQ ID NO:365); mmu-mir-216a, UUGGUUUAAUCUCAGCUGGCAACUGUGAGAUGUCCCUAUCAUUCCUCA CAGUGGUCUCUGGGAUUAUGCUAA (MI0000699, SEQ ID NO:366); mmu-mir-216b, UUGGCAGACUGGGAAAUCUCUGCAGGCAAAUGUGAUGUCACUGAAGAA ACCACACACUUACCUGUAGAGAUUCUUCAGUCUGACAA (MI0004126, SEQ ID NO:367); ppa-mir-216, GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAACU GUGAGAUGUUCAUACAAUCCCUCACAGUGGUCUCUGGGAUUAUGCUAA ACAGAGCAAUUUCCUAGCCCUCACGA (MI0002865, SEQ ID NO:368); ppy-mir-216, GAUGGCUGUGAGUUGGCUUAAUCUCAGCUGGCAACUGUGAGAUGUUCA UACAAUCCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUU CCUUGCCCUCACGA (MI0002864, SEQ ID NO:369); ptr-mir-216, GAUGGCUGUGAGUUGGCUUAUCUCAGCUGGCAACUGUGAGAUGUUCAU ACAAUCCCUCACAGUGGUCUCUGGGAUUAAACUAAACAGAGCAAUUUC CUAGCCCUCACGA (MI0002862, SEQ ID NO:370); rno-mir-216, GUUAGC UAUGAGUUAGUUUAAUCUCAGCUGGCAACUGUGAGAUGUCCCUAUCAU UCCUCACAGUGGUCUCUGGGAUUAUGCUAAACAGAGCAAUUUCCUUGA CCUC (MI0000955, SEQ ID NO:371); ssc-mir-216, GAUGGCUGUGAGUUG GCUUAAUCUCAGCUGGCAACUGUGAGAUGUUCAUACAAUCCCCCACAGU GGUCUCUGGGAUUAUGCUAAACAGAGCAAUUUCCUUGCCCU (MI0002424, SEQ ID NO:372); tni-mir-216a, UUGGUGAAAUCUCAGCUGGCAACUGUGAGUCG UUCACUAGCUGCUCUCACAAUGGCCUCUGGGAUUAUGCUAA (MI0003292, SEQ ID NO:373); tni-mir-216b, UGACUGUUUAAUCUCUGCAGGCAAC UGUGAUGGUGAUUUUUAUUCUCACAAUCACCUGGAGAGAUUCUGCAGU UUAU (MI0003294, SEQ ID NO:374); xtr-mir-216, UGGCUGUGAAUUGGCUUAAU CUCAGCUGGCAACUGUGAGCAGUUAAUAAAUUAUCUCACAGUGGUCUC UGGGAUUAUACUAAACACAGCAA (MI0004869, SEQ ID NO:375) or complement thereof.

Stem-loop sequences of miR-331, family members include hsa-mir-331, GAGUUUGGUUUUGUUUGGGUUUGUUCUAGGUAUGGUCCCAGGGAUCCC AGAUCAAACCAGGCCCCUGGGCCUAUCCUAGAACCAACCUAAGCUC (MI0000812, SEQ ID NO:376); bta-mir-331, GAGUUUGGUUUUGUU UGGGUUUGUUCUAGGUAUGGUCCCAGGGAUCCCAGAUCAAACCAGGCC CCUGGGCCUAUCCUAGAACCAACCUAA (MI0005463, SEQ ID NO:377); mmu-mir-331, GAGUCUGGUUUUGUUUGGGUUUGUUCUAGGUAUGGUCCCAGGGAU CCCAGAUCAAACCAGGCCCCUGGGCCUAUCCUAGAACCAACCUAAACCC GU (MI0000609, SEQ ID NO:378); rno-mir-331, GAGUCUGGUCUUG UUUGGGUUUGUUCUAGGUAUGGUCCCAGGGAUCCCAGAUCAAACCAGG CCCCUGGGCCUAUCCUAGAACCAACCUAAACCCAU (MI0000608, SEQ ID NO:379) or complement thereof.

Stem-loop sequences of miR-292-3p family members include mmu-mir-292, CAGCCUGUGAUACUCAAACUGGGGGCUCUUUUGGAUUUUCAUCGGAAG AAAAGUGCCGCCAGGUUUUGAGUGUCACCGGUUG (MI0000390, SEQ ID NO:380); hsa-mir-371, GUGGCACUCAAACUGUGGGGGCACUUUCUGCUCUCUGG UGAAAGUGCCGCCAUCUUUUGAGUGUUAC (MI0000779, SEQ ID NO:381); hsa-mir-372, GUGGGCCUCAAAUGUGGAGCACUAUUCUGAUGUCCAAGUGG AAAGUGCUGCGACAUUUGAGCGUCAC (MI0000780, SEQ ID NO:382); mmu-mir-290, CUCAUCUUGCGGUACUCAAACUAUGGGGGCACUUUUUUUUUUCUU UAAAAAGUGCCGCCUAGUUUUAAGCCCCGCCGGUUGAG (MI0000388, SEQ ID NO:383); mmu-mir-291a, CCUAUGUAGCGGCCAUCAAAGUGGAGGCCCUCUCU UGAGCCUGAAUGAGAAAGUGCUUCCACUUUGUGUGCCACUGCAUGGG (MI0000389, SEQ ID NO:384); mmu-mir-291b, ACAUACAGUGUCGAUCAAAGUGGAGGCCCUCUCCGCGGCUUGGCGGGA AAGUGCAUCCAUUUUGUUUGUCUCUGUGUGU (MI0003539, SEQ ID NO:385); mmu-mir-293, UUCAAUCUGUGGUACUCAAACUGUGUGACAUUUUG UUCUUUGUAAGAAGUGCCGCAGAGUUUGUAGUGUUGCCGAUUGAG

(MI0000391, SEQ ID NO:386); mmu-mir-294, UUCCAUAUAGCCA UACUCAAAAUGGAGGCCCUAUCUAAGCUUUUAAGUGGAAAGUGCUUCC CUUUUGUGUGUUGCCAUGUGGAG (MI0000392, SEQ ID NO:387); mmu-mir-295,
GGUGAGACUCAAAUGUGGGGCACACUUCUGGACUGUACAUAGAAAGUG CUACUACUUUUGAGUCUCUCC (MI0000393, SEQ ID NO:388); rno-mir-290, UCAUCUUGCGGUUCUCAAACUAUGGGGGCACUUUUUUUUUCUUUAAAA AGUGCCGCCAGGUUUUAGGGCCUGCCGGUUGAG (MI0000964, SEQ ID NO:389); rno-mir-291,
CCGGUGUAGUAGCCAUCAAAGUGGAGGCCCUCUCUUG
GGCCCGAGCUAGAAAGUGCUUCCACUUUGUGUGCCACUGCAUGGG (MI0000965, SEQ ID NO:390); rno-mir-292, CAACCUGUGAUACUCAAACUGGGGGCUCUUUUGGGUUUUCUUUGGAAG AAAAGUGCCGCCAGGUUUUGAGUGUUACCGAUUG, MI0000966, SEQ ID NO:391) or a complement thereof.

In a further aspect, "a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence" generally includes all or a segment of the full length precursor of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p family members.

In certain aspects, a nucleic acid miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid, or a segment or a mimetic thereof, will comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more nucleotides of the precursor miRNA or its processed sequence, including all ranges and integers there between. In certain embodiments, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence contains the full-length processed miRNA sequence and is referred to as the "miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p full-length processed nucleic acid sequence." In still further aspects, a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p comprises at least one 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, 21, 22, 23, 24, 25, 50 nucleotide (including all ranges and integers there between) segment of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p that is at least 75, 80, 85, 90, 95, 98, 99 or 100% identical to SEQ ID NOs provided herein.

In specific embodiments, a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor containing nucleic acid is miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor, or a variation thereof. miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p can be hsa-miR-15, hsa-miR-26, hsa-miR-31, hsa-miR-145, hsa-miR-147, hsa-miR-188, hsa-miR-215, hsa-miR-216, hsa-miR-331, or mmu-miR-292-3p, respectively.

In a further aspect, a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor can be administered with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more miRNAs or miRNA inhibitors. miRNAs or their complements can be administer concurrently, in sequence or in an ordered progression. In certain aspects, a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor can be administered in combination with one or more of let-7, miR-15, miR-16, miR-20, miR-21, miR-26a, miR-34a, miR-126, miR-143, miR-147, miR-188, miR-200, miR-215, miR-216, miR-292-3p, and/or miR-331 nucleic acids or inhibitors thereof. All or combinations of miRNAs or inhibitors thereof may be administered in a single formulation. Administration may be before, during or after a second therapy.

miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acids or complement thereof may also include various heterologous nucleic acid sequence, *i.e.,* those sequences not typically found operatively coupled with miR-15, miR-26, miR-31, miR-145, miR-147, miR-188,

miR-215, miR-216, miR-331, or mmu-miR-292-3p in nature, such as promoters, enhancers, and the like. The miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid is a recombinant nucleic acid, and can be a ribonucleic acid or a deoxyribonucleic acid. The recombinant nucleic acid may comprise a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor expression cassette, *i.e.*, a nucleic acid segment that expresses a nucleic acid when introduce into an environment containing components for nucleic acid synthesis. In a further aspect, the expression cassette is comprised in a viral vector, or plasmid DNA vector or other therapeutic nucleic acid vector or delivery vehicle, including liposomes and the like. In a particular aspect, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid is a synthetic nucleic acid. Moreover, nucleic acids of the invention may be fully or partially synthetic. In certain aspects, viral vectors can be administered at $1x10^2$, $1x10^3$, $1x10^4$ $1x10^5$, $1x10^6$, $1x10^7$, $1x10^8$, $1x10^9$, $1x10^{10}$, $1x10^{11}$, $1x10^{12}$, $1x10^{13}$, $1x10^{14}$ pfu or viral particle (vp).

In a particular aspect, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor is a synthetic nucleic acid. Moreover, nucleic acids of the invention may be fully or partially synthetic. In still further aspects, a nucleic acid of the invention or a DNA encoding a nucleic acid of the invention can be administered at 0.001, 0.01, 0.1, 1, 10, 20, 30, 40, 50, 100, 200, 400, 600, 800, 1000, 2000, to 4000 μg or mg, including all values and ranges there between. In yet a further aspect, nucleic acids of the invention, including synthetic nucleic acid, can be administered at 0.001, 0.01, 0.1, 1, 10, 20, 30, 40, 50, 100, to 200 μg or mg per kilogram (kg) of body weight. Each of the amounts described herein may be administered over a period of time, including 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, minutes, hours, days, weeks, months or years, including all values and ranges there between.

In certain embodiments, administration of the composition(s) can be enteral or parenteral. In certain aspects, enteral administration is oral. In further aspects,

parenteral administration is intralesional, intravascular, intracranial, intrapleural, intratumoral, intraperitoneal, intramuscular, intralymphatic, intraglandular, subcutaneous, topical, intrabronchial, intratracheal, intranasal, inhaled, or instilled. Compositions of the invention may be administered regionally or locally and not necessarily directly into a lesion.

In certain aspects, the gene or genes modulated comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200 or more genes or combinations of genes identified in Tables 1, 3, and/or 4. In still further aspects, the gene or genes modulated may exclude 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 175 or more genes or combinations of genes identified in Tables 1, 3, and/or 4. Modulation includes modulating transcription, mRNA levels, mRNA translation, and/or protein levels in a cell, tissue, or organ. In certain aspects the expression of a gene or level of a gene product, such as mRNA or encoded protein, is down-regulated or up-regulated. In a particular aspect the gene modulated comprises or is selected from (and may even exclude) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26. 27, 28, or all of the genes identified in Tables 1, 3, and/or 4, or any combinations thereof. In certain embodiments a gene modulated or selected to be modulated is from Table 1. In further embodiments a gene modulated or selected to be modulated is from Table 3. In still further embodiments a gene modulated or selected to be modulated is from Table 4. In certain aspects of the invention one or more genes may be excluded from the claimed invention.

Embodiments of the invention may also include obtaining or assessing a gene expression profile or miRNA profile of a target cell prior to selecting the mode of treatment, *e.g.*, administration of a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid, inhibitor of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or mimetics thereof.. The database content related to all nucleic acids and genes designated by an accession number or a database submission are incorporated herein by reference as of the filing date of this application. In certain aspects of the invention one or more miRNA or miRNA inhibitor may modulate a single gene. In a further aspect, one or more genes in one or more genetic, cellular, or

physiologic pathways can be modulated by one or more miRNAs or complements thereof, including miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acids in combination with other miRNAs.

A further embodiment of the invention is directed to methods of modulating a cellular pathway comprising administering to the cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acids and miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitors in combination with other miRNAs or miRNA inhibitors.

miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acids may also include various heterologous nucleic acid sequence, *i.e.,* those sequences not typically found operatively coupled with miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p in nature, such as promoters, enhancers, and the like. The miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid is a recombinant nucleic acid, and can be a ribonucleic acid or a deoxyribonucleic acid. The recombinant nucleic acid may comprise a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p expression cassette. In a further aspect, the expression cassette is comprised in a viral, or plasmid DNA vector or other therapeutic nucleic acid vector or delivery vehicle, including liposomes and the like. In a particular aspect, the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid is a synthetic nucleic acid. Moreover, nucleic acids of the invention may be fully or partially synthetic.

A further embodiment of the invention is directed to methods of modulating a cellular pathway comprising administering to the cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence in an amount sufficient to modulate the expression, function, status, or state of a cellular pathway, in particular those pathways described in Table 2 or the pathways known to include one or more genes from Table 1, 3, and/or 4. Modulation of a cellular pathway

includes, but is not limited to modulating the expression of one or more gene. Modulation of a gene can include inhibiting the function of an endogenous miRNA or providing a functional miRNA to a cell, tissue, or subject. Modulation refers to the expression levels or activities of a gene or its related gene product or protein, *e.g.*, the mRNA levels may be modulated or the translation of an mRNA may be modulated, etc. Modulation may increase or up regulate a gene or gene product or it may decrease or down regulate a gene or gene product.

Still a further embodiment includes methods of treating a patient with a pathological condition comprising one or more of step (a) administering to the patient an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence in an amount sufficient to modulate the expression of a cellular pathway; and (b) administering a second therapy, wherein the modulation of the cellular pathway sensitizes the patient to the second therapy. A cellular pathway may include, but is not limited to one or more pathway described in Table 2 below or a pathway that is know to include one or more genes of Tables 1, 3, and/or 4. A second therapy can include administration of a second miRNA or therapeutic nucleic acid, or may include various standard therapies, such as chemotherapy, radiation therapy, drug therapy, immunotherapy, and the like. Embodiments of the invention may also include the determination or assessment of a gene expression profile for the selection of an appropriate therapy.

Embodiments of the invention include methods of treating a subject with a pathological condition comprising one or more of the steps of (a) determining an expression profile of one or more genes selected from Table 1, 3, and/or 4; (b) assessing the sensitivity of the subject to therapy based on the expression profile; (c) selecting a therapy based on the assessed sensitivity; and (d) treating the subject using selected therapy. Typically, the pathological condition will have as a component, indicator, or result the mis-regulation of one or more gene of Table 1, 3, and/or 4.

Further embodiments include the identification and assessment of an expression profile indicative of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p status in a cell or tissue

comprising expression assessment of one or more gene from Table 1, 3, and/or 4, or any combination thereof.

The term "miRNA" is used according to its ordinary and plain meaning and refers to a microRNA molecule found in eukaryotes that is involved in RNA-based gene regulation. See, *e.g.*, Carrington *et al.*, 2003, which is hereby incorporated by reference. The term can be used to refer to the single-stranded RNA molecule processed from a precursor or in certain instances the precursor itself.

In some embodiments, it may be useful to know whether a cell expresses a particular miRNA endogenously or whether such expression is affected under particular conditions or when it is in a particular disease state. Thus, in some embodiments of the invention, methods include assaying a cell or a sample containing a cell for the presence of one or more marker gene or mRNA or other analyte indicative of the expression level of a gene of interest. Consequently, in some embodiments, methods include a step of generating an RNA profile for a sample. The term "RNA profile" or "gene expression profile" refers to a set of data regarding the expression pattern for one or more gene or genetic marker in the sample (*e.g.*, a plurality of nucleic acid probes that identify one or more markers from Tables 1, 3, and/or 4); it is contemplated that the nucleic acid profile can be obtained using a set of RNAs, using for example nucleic acid amplification or hybridization techniques well know to one of ordinary skill in the art. The difference in the expression profile in the sample from the patient and a reference expression profile, such as an expression profile from a normal or non-pathologic sample, is indicative of a pathologic, disease, or cancerous condition. A nucleic acid or probe set comprising or identifying a segment of a corresponding mRNA can include all or part of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 ,13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 100, 200, 500, or more nucleotides, including any integer or range derivable there between, of a gene, or genetic marker, or a nucleic acid, mRNA or a probe representative thereof that is listed in Tables 1, 3, and/or 4, or identified by the methods described herein.

Certain embodiments of the invention are directed to compositions and methods for assessing, prognosing, or treating a pathological condition in a patient

comprising measuring or determining an expression profile of one or more marker(s) in a sample from the patient, wherein a difference in the expression profile in the sample from the patient and an expression profile of a normal sample or reference expression profile is indicative of pathological condition and particularly cancer. In certain aspects of the invention, the cellular pathway, gene, or genetic marker is or is representative of one or more pathway or marker described in Table 1, 3, and/or 4, including any combination thereof.

Aspects of the invention include diagnosing, assessing, or treating a pathologic condition or preventing a pathologic condition from manifesting. For example, the methods can be used to screen for a pathological condition; assess prognosis of a pathological condition; stage a pathological condition; assess response of a pathological condition to therapy; or to modulate the expression of a gene, genes, or related pathway as a first therapy or to render a subject sensitive or more responsive to a second therapy. In particular aspects, assessing the pathological condition of the patient can be assessing prognosis of the patient. Prognosis may include, but is not limited to an estimation of the time or expected time of survival, assessment of response to a therapy, and the like. In certain aspects, the altered expression of one or more gene or marker is prognostic for a patient having a pathologic condition, wherein the marker is one or more of Table 1, 3, and/or 4, including any combination thereof.

Table 1A. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-15a

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	$\Delta \log_2$
ABCA1	NM_005502	0.706584
ABCB6 /// ATG9A	NM_005689 /// NM_024085	-0.893191
ABLIM3	NM_014945	0.807167
ACOX2	NM_003500	-0.884661
ADARB1	NM_001033049 /// NM_001112 /// NM_015833 /// NM_015834	1.67209
ADM	NM_001124	0.982052
ADRB2	NM_000024	1.04898
AKAP12	NM_005100 /// NM_144497	0.807181
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	1.07515
ANKRD46	NM_198401	0.725941
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	0.951172
AOX1	NM_001159	1.27456
AP1S2	NM_003916	0.722522

APOH	NM_000042	-0.778363
APP	NM_000484 /// NM_201413 /// NM_201414	0.710494
AQP3	NM_004925	-1.0108
ARHGDIA	NM_004309	-1.43641
ARHGDIB	NM_001175	0.829838
ARL2	NM_001667	-1.94907
ARL2BP	NM_012106	1.20234
ATP6V0E	NM_003945	1.30096
AXL	NM_001699 /// NM_021913	1.26935
BAG5	NM_001015048 /// NM_001015049 /// NM_004873	-0.731695
BAMBI	NM_012342	-0.882718
BCL2A1	NM_004049	0.801198
BEAN	XM_375359	1.14936
BIRC3	NM_001165 /// NM_182962	0.984482
BTN3A2	NM_007047	0.819101
C4BPB	NM_000716 /// NM_001017364 /// NM_001017365 ///NM_001017366 /// NM_001017367	2.02325
C6orf216	NM_206908 /// NM_206910 /// NM_206911 /// NM_206912 /// XR_000259	1.05448
C8orf1	NM_004337	-0.702374
CA12	NM_001218 /// NM_206925	-1.26277
CCL20	NM_004591	0.853408
CCND1	NM_053056	-0.889303
CCND3	NM_001760	-1.05519
CCNG2	NM_004354	1.00993
CDC37L1	NM_017913	-0.876288
CDCA4	NM_017955 /// NM_145701	-0.773713
CDH17	NM_004063	-1.09072
CDH4	NM_001794	0.830142
CDKN2C	NM_001262 /// NM_078626	-1.00104
CDS2	NM_003818	-1.19113
CFH /// CFHL1	NM_000186 /// NM_001014975 /// NM_002113	-0.888088
CGI-38	NM_015964 /// NM_016140	-0.758479
CGI-48	NM_016001	1.58316
CHAF1A	NM_005483	-0.714709
CHUK	NM_001278	-1.04118
CLCN4	NM_001830	-0.915403
CLIC4	NM_013943	0.899491
COL11A1	NM_001854 /// NM_080629 /// NM_080630	1.21281
COL4A1	NM_001845	0.721033
COL4A2	NM_001846	0.752816
COL5A1	NM_000093	0.781154
COL6A1	NM_001848	0.708164
CPM	NM_001005502 /// NM_001874 /// NM_198320	1.03293
CTGF	NM_001901	1.44017
CTSS	NM_004079	0.753473
CXCL1	NM_001511	1.13774
CXCL2	NM_002089	0.914747
CXCL5	NM_002994	0.832592
CXCR4	NM_001008540 /// NM_003467	0.946256
CYP4F11	NM_021187	-1.17394
CYP4F3	NM_000896	-1.39695

CYR61	NM_001554	0.801016
DAAM1	NM_014992	1.11752
DAF	NM_000574	0.749996
DDAH1	NM_012137	1.11882
DHPS	NM_001930 /// NM_013406 /// NM_013407	-0.749475
DIO2	NM_000793 /// NM_001007023 /// NM_013989	1.05322
DOCK4	NM_014705	0.715045
DSU	NM_018000	0.832877
DUSP1	NM_004417	0.901714
DUSP10	NM_007207 /// NM_144728 /// NM_144729	0.802771
DUSP5	NM_004419	1.06893
DUSP6	NM_001946 /// NM_022652	0.762807
E2F8	NM_024680	-1.09486
EEF1D	NM_001960 /// NM_032378	1.09981
EFEMP1	NM_004105 /// NM_018894	1.53793
EIF4E	NM_001968	-0.706986
ENO1	NM_001428	1.06282
EPAS1	NM_001430	1.14112
FAM18B	NM_016078	-0.710266
FBN1	NM_000138	0.864655
FBXO11	NM_012167 /// NM_018693 /// NM_025133	1.10195
FGF2	NM_002006	-1.38337
FGFR4	NM_002011 /// NM_022963 /// NM_213647	-0.706112
FKBP1B	NM_004116 /// NM_054033	-0.953076
FLJ13910	NM_022780	0.733455
FNBP1	NM_015033	0.943991
FSTL1	NM_007085	0.814388
GALNT7	NM_017423	-1.08105
GBP1	NM_002053	0.94431
GCLC	NM_001498	-0.735984
GFPT1	NM_002056	-0.88304
GLIPR1	NM_006851	0.739398
GTSE1	NM_016426	-0.789888
HAS2	NM_005328	-0.875224
HEG	XM_087386	0.947872
HMGA2	NM_001015886 /// NM_003483 /// NM_003484	1.10974
HMGCS1	NM_002130	1.13726
HSPA1B	NM_005346	-1.2135
IER3IP1	NM_016097	1.02762
IFI16	NM_005531	1.10866
IGFBP3	NM_000598 /// NM_001013398	0.767581
IL6	NM_000600	1.18471
IL6ST	NM_002184 /// NM_175767	0.726757
IL8	NM_000584	1.10422
INHBB	NM_002193	-0.950023
INHBC	NM_005538	0.898337
INSIG1	NM_005542 /// NM_198336 /// NM_198337	0.74226
INSL4	NM_002195	-1.11623
IQGAP2	NM_006633	-0.783372
IRF1	NM_002198	0.72684
ITPR2	NM_002223	0.740631
KCNJ2	NM_000891	1.35987

KIAA0485	---	1.10255
KIAA0754	---	0.899045
KLF4	NM_004235	-0.749759
KRT7	NM_005556	1.21091
LAMC2	NM_005562 /// NM_018891	0.733084
LCN2	NM_005564	-0.794915
LOC153561	NM_207331	0.794392
LOC348162	XM_496132	0.774096
LOXL2	NM_002318	0.740607
LRP12	NM_013437	-0.784206
LYPD1	NM_144586	1.24908
MAP3K2	NM_006609	0.733667
MAP7	NM_003980	-1.16472
MAZ	NM_002383	-0.725569
MCL1	NM_021960 /// NM_182763	1.65586
MEG3	XR_000167 /// XR_000277	0.800336
MGC5618	---	0.912493
MPPE1	NM_023075 /// NM_138608	-0.72104
MYL9	NM_006097 /// NM_181526	0.795096
NALP1	NM_001033053 /// NM_014922 /// NM_033004 /// NM_033006 /// NM_033007	1.06065
NAV3	NM_014903	0.773472
NF1	NM_000267	-1.44283
NFE2L3	NM_004289	0.884419
NFKB2	NM_002502	0.773655
NID1	NM_002508	0.892766
NMT2	NM_004808	0.828083
NNMT	NM_006169	1.1372
NPC1	NM_000271	1.36826
NTE	NM_006702	-0.726337
NUCKS	NM_022731	2.22615
NUPL1	NM_001008564 /// NM_001008565 /// NM_014089	-0.806715
PDZK1IP1	NM_005764	1.08475
PFAAP5	NM_014887	0.792392
PGK1	NM_000291	1.87681
PHACTR2	NM_014721	-0.81188
PLA2G4A	NM_024420	-0.87476
PLSCR4	NM_020353	-1.89975
PMCH	NM_002674	1.04416
PNMA2	NM_007257	0.704085
PODXL	NM_001018111 /// NM_005397	1.257
PPP1R11	NM_021959 /// NM_170781	-0.806236
PRO1843	---	1.19666
PTENP1	---	1.07135
PTGS2	NM_000963	-1.0791
PTK9	NM_002822 /// NM_198974	1.20386
PTPRE	NM_006504 /// NM_130435	0.703589
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.73124
RAB2	NM_002865	1.39501
RAFTLIN	NM_015150	1.67418
RARRES3	NM_004585	0.757518

RASGRP1	NM_005739	1.08021
RBL1	NM_002895 /// NM_183404	-0.842142
RDX	NM_002906	0.700954
RGS2	NM_002923	0.823743
RHEB	NM_005614	1.07333
RIP	NM_001033002 /// NM_032308	1.51241
ROR1	NM_005012	0.824907
RPL14	NM_001034996 /// NM_003973	0.969345
RPL38	NM_000999	1.50078
RPS11	NM_001015	1.37758
RPS6KA3	NM_004586	-1.21197
RPS6KA5	NM_004755 /// NM_182398	0.938506
S100P	NM_005980	-1.06668
SEMA3C	NM_006379	0.845374
SEPT6 /// N-PAC	NM_015129 /// NM_032569 /// NM_145799 /// NM_145800 /// NM_145802	1.04331
SKP2	NM_005983 /// NM_032637	0.74694
SLC11A2	NM_000617	-1.0072
SLC26A2	NM_000112	0.711837
SMA4	NM_021652	0.789119
SMARCA2	NM_003070 /// NM_139045	1.09406
SNAI2	NM_003068	0.817633
SNAP23	NM_003825 /// NM_130798	0.815178
SOCS2	NM_003877	0.886257
SPARC	NM_003118	1.44472
SPFH2	NM_001003790 /// NM_001003791 /// NM_007175	-0.730905
SPOCK	NM_004598	0.834427
STC1	NM_003155	1.05196
STX3A	NM_004177	0.910285
SULT1C1	NM_001056 /// NM_176825	0.793242
SUMO2	NM_001005849 /// NM_006937	0.867526
SYNE1	NM_015293 /// NM_033071 /// NM_133650 /// NM_182961	1.33924
TACC1	NM_006283	-1.05059
TAF15	NM_003487 /// NM_139215	0.941963
TAGLN	NM_001001522 /// NM_003186	1.54875
TFG	NM_001007565 /// NM_006070	0.894314
THBD	NM_000361	1.18344
THBS1	NM_003246	-0.871039
THUMPD1	NM_017736	-0.772288
TM7SF1	NM_003272	0.879449
TMEM45A	NM_018004	-0.851551
TNFAIP6	NM_007115	0.758707
TNFSF9	NM_003811	-1.51814
TOP1	NM_003286	0.717449
TOX	NM_014729	1.57101
TPM1	NM_000366 /// NM_001018004 /// NM_001018005 /// NM_001018006 /// NM_001018007 //	1.07102
TRA1	NM_003299	2.20518
TRIM22	NM_006074	1.39642
TRIO	NM_007118	0.767064
TTC3	NM_001001894 /// NM_003316	0.713917

TTMP	NM_024616	1.06102
TUBB4	NM_006087	-0.757438
TXN	NM_003329	1.62493
UBE2I	NM_003345 /// NM_194259 ///NM_194260 /// NM_194261	0.882595
UBE2L6	NM_004223 /// NM_198183	0.84659
UGCG	NM_003358	0.848697
USP34	NM_014709	1.0433
VAV3	NM_006113	-0.868484
VDAC3	NM_005662	1.05842
VIL2	NM_003379	1.03829
VPS4A	NM_013245	-0.876444
VTI1B	NM_006370	-1.07453
WISP2	NM_003881	0.998185
WNT7B	NM_058238	-0.81257
WSB2	NM_018639	0.835972
XTP2	NM_015172	1.07659
YRDC	NM_024640	-0.747991
ZBED2	NM_024508	1.17703

Table 1B. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-26.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	$\Delta \log_2$
ABR	NM_001092 /// NM_021962	-0.833053
ACTR2	NM_001005386 /// NM_005722	0.784523
AER61	NM_173654	1.17093
AHNAK	NM_001620 /// NM_024060	-1.19295
AKAP12	NM_005100 /// NM_144497	0.869987
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	0.815452
ALDH5A1	NM_001080 /// NM_170740	-1.37495
ANKRD12	NM_015208	1.0142
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	1.41894
ARFRP1	NM_003224	-0.72603
ARG2	NM_001172	0.886422
ARHGDIA	NM_004309	-1.08013
ARHGDIB	NM_001175	1.17986
ARL2BP	NM_012106	0.975481
ARTS-1	NM_016442	0.747895
ATP6V0E	NM_003945	1.10054
ATP9A	NM_006045	-0.960651
AXL	NM_001699 /// NM_021913	1.36117
B4GALT4	NM_003778 /// NM_212543	-1.0873
BCAT1	NM_005504	1.00482
BCL2L1	NM_001191 /// NM_138578	-1.45177
BID	NM_001196 /// NM_197966 /// NM_197967	-1.04896
BNC2	NM_017637	1.2229
C14orf10	NM_017917	-1.11148
C1orf116	NM_023938	-0.834587
C1orf24	NM_022083 /// NM_052966	1.15962
C1R	NM_001733	0.83181

C2orf23	NM_022912	1.15358
C3	NM_000064	0.78698
C4BPB	NM_000716 /// NM_001017364 /// NM_001017365 /// NM_001017366 /// NM_001017367	0.992525
C5orf13	NM_004772	0.966799
C6orf210	NM_020381	-0.820329
C6orf216	NM_206908 /// NM_206910 /// NM_206911 /// NM_206912 /// XR_000259	1.04882
C8orf1	NM_004337	-1.30736
CA12	NM_001218 /// NM_206925	-0.904882
CCDC28A	NM_015439	-1.62476
CCL2	NM_002982	0.911105
CDH1	NM_004360	-1.13232
CDH4	NM_001794	-0.745807
CDK8	NM_001260	-1.16149
CFH	NM_000186 /// NM_001014975	0.968934
CGI-38	NM_015964 /// NM_016140	-0.742848
CGI-48	NM_016001	1.0641
CHAF1A	NM_005483	-0.939655
CHGB	NM_001819	0.920022
CHORDC1	NM_012124	-1.22107
CLDN3	NM_001306	-0.982855
CLGN	NM_004362	1.28034
CLIC4	NM_013943	1.37928
CLU	NM_001831 /// NM_203339	1.18464
CMKOR1	NM_020311	0.74412
COL11A1	NM_001854 /// NM_080629 /// NM_080630	0.813938
COL13A1	NM_005203 /// NM_080798 /// NM_080799 /// NM_080800 /// NM_080801 /// NM_080802	1.16345
COL1A1	NM_000088	0.821137
COL3A1	NM_000090	1.09758
COL6A1	NM_001848	0.968416
COMMD8	NM_017845	-1.05693
CPE	NM_001873	1.07766
CREBL2	NM_001310	-1.79105
CRIP2	NM_001312	-1.11007
CSPG2	NM_004385	-0.911751
CTGF	NM_001901	1.25393
CTNND1	NM_001331	-0.715801
CXCL1	NM_001511	0.845021
CXCL2	NM_002089	1.01158
CXCL5	NM_002994	0.704588
CYP1B1	NM_000104	0.828644
CYP3A5	NM_000777	0.703318
CYR61	NM_001554	0.764686
DAAM1	NM_014992	0.976142
DAF	NM_000574	0.76146
DAPK3	NM_001348	-0.779372
DHPS	NM_001930 /// NM_013406 /// NM_013407	-1.00747
DHRS2	NM_005794 /// NM_182908	1.43654
DIO2	NM_000793 /// NM_001007023 /// NM_013989	0.791523
DKFZP564F0522	NM_015475	-1.0877

DPYD	NM_000110	1.41139
DST	NM_001723 /// NM_015548 /// NM_020388 /// NM_183380	-0.836643
DZIP1	NM_014934 /// NM_198968	1.03592
E2F5	NM_001951	-0.796317
E2F8	NM_024680	1.00205
EEF1D	NM_001960 /// NM_032378	0.703203
EFEMP1	NM_004105 /// NM_018894	1.4837
EHD1	NM_006795	-0.910559
EIF2C2	NM_012154	1.09581
EIF2S1	NM_004094	-1.88674
EIF4E	NM_001968	-1.2231
ELF3	NM_004433	-0.780173
ENPP4	NM_014936	1.19671
EPB41L1	NM_012156 /// NM_177996	-1.12118
EPHA2	NM_004431	-1.07269
F3	NM_001993	1.31706
FA2H	NM_024306	-1.34489
FAS	NM_000043 /// NM_152871 /// NM_152872 /// NM_152873 /// NM_152874 /// NM_152875	0.748072
FBN1	NM_000138	0.87804
FBXO11	NM_012167 /// NM_018693 /// NM_025133	1.06424
FBXW2	NM_012164	-1.05455
FDXR	NM_004110 /// NM_024417	-0.723062
FGB	NM_005141	1.38093
FLJ13910	NM_022780	1.05579
FLJ20035	NM_017631	0.859671
FLJ21159	NM_024826	-0.829431
FLOT2	NM_004475	-0.708745
FOXD1	NM_004472	1.05024
FSTL1	NM_007085	0.989345
FXYD2	NM_001680 /// NM_021603	-1.16617
FZD7	NM_003507	1.06154
G0S2	NM_015714	0.906439
GABRA5	NM_000810	0.750404
GALC	NM_000153	0.936774
GATA6	NM_005257	1.09725
GCH1	NM_000161 /// NM_001024024 /// NM_001024070 /// NM_001024071	0.891087
GFPT2	NM_005110	0.913412
GGT1	NM_001032364 /// NM_001032365 /// NM_005265 /// NM_013430	-0.712035
GLIPR1	NM_006851	2.13759
GLUL	NM_001033044 /// NM_001033056 /// NM_002065	-0.849756
GMDS	NM_001500	-2.14521
GOLPH4	NM_014498	0.95472
GPR64	NM_005756	0.771741
GRB10	NM_001001549 /// NM_001001550 /// NM_001001555 /// NM_005311	-1.03799
HAS2	NM_005328	0.731898
HECTD3	NM_024602	-1.23335
HES1	NM_005524	0.825981

HIC2	NM_015094	0.785963
HIST1H3H	NM_003536	-0.823929
HKDC1	NM_025130	-1.33618
HMGA1	NM_002131 /// NM_145899 /// NM_145901 /// NM_145902 /// NM_145903 /// NM_145904	-1.408
HMGA2	NM_001015886 /// NM_003483 /// NM_003484	-0.91126
HNMT	NM_001024074 /// NM_001024075 /// NM_006895	0.734274
HOXA10	NM_018951 /// NM_153715	0.834274
HSPG2	NM_005529	-0.747033
HUMPPA	NM_014603	-1.38414
IDS	NM_000202 /// NM_006123	-0.798159
IER3IP1	NM_016097	0.804619
IFI16	NM_005531	0.942019
IFIT1	NM_001001887 /// NM_001548	-0.752143
IGFBP1	NM_000596 /// NM_001013029	-0.79273
IGFBP3	NM_000598 /// NM_001013398	0.842426
IL15	NM_000585 /// NM_172174 /// NM_172175	1.07245
IL27RA	NM_004843	1.30764
IL6R	NM_000565 /// NM_181359	0.896767
IL6ST	NM_002184 /// NM_175767	0.939897
IL8	NM_000584	1.09477
INHBB	NM_002193	-1.52081
ITGB4	NM_000213 /// NM_001005619 /// NM_001005731	-1.21785
ITPR2	NM_002223	0.746339
KCNK3	NM_002246	1.55402
KDELC1	NM_024089	1.18441
KIAA0152	NM_014730	-0.941345
KIAA0485	---	1.07753
KIAA0527	XM_171054	1.96041
KIAA0830	XM_290546	1.06806
LEPR	NM_001003679 /// NM_001003680 /// NM_002303	-0.770574
LHX2	NM_004789	1.22767
LMNB1	NM_005573	1.19247
LOC153561	NM_207331	0.764558
LOC389435	XM_371853	0.810852
LOC93349	NM_138402	0.812908
LOXL2	NM_002318	-1.38541
LUM	NM_002345	1.1044
LYPD1	NM_144586	0.815066
MAPK6	NM_002748	-1.20395
MATN3	NM_002381	-1.34865
MAZ	NM_002383	-1.00548
MCAM	NM_006500	0.723075
MCL1	NM_021960 /// NM_182763	1.13287
METAP2	NM_006838	-1.14678
MGC35048	NM_153208	-0.946659
MGC4707	NM_001003676 /// NM_001003677 /// NM_001003678 /// NM_024113	-1.05407
MRS2L	NM_020662	-0.910868
MTX2	NM_001006635 /// NM_006554	-1.18578
MVP	NM_005115 /// NM_017458	-1.2441
MYBL1	XM_034274	0.740775

MYCBP	NM_012333	-1.57357
MYL9	NM_006097 /// NM_181526	1.76885
NAB1	NM_005966	-0.838872
NID1	NM_002508	0.705762
NID2	NM_007361	1.93735
NR2F1	NM_005654	1.07657
NR4A2	NM_006186 /// NM_173171 /// NM_173172 /// NM_173173	0.839422
NR5A2	NM_003822 /// NM_205860	-0.738757
NRG1	NM_004495 /// NM_013956 /// NM_013957 /// NM_013958 /// NM_013959 /// NM_013960	-1.15784
NRIP1	NM_003489	1.05135
NT5E	NM_002526	1.0583
NTE	NM_006702	-1.02896
NUCKS	NM_022731	1.85433
OLFM1	NM_006334 /// NM_014279 /// NM_058199	1.11853
PAPPA	NM_002581	1.06925
PBX1	NM_002585	0.715565
PDCD4	NM_014456 /// NM_145341	0.832384
PDE4D	NM_006203	0.756904
PDGFRL	NM_006207	1.1499
PDK4	NM_002612	0.705278
PDXK	NM_003681	-1.40137
PDZK1	NM_002614	-1.0713
PEG10	XM_496907 /// XM_499343	1.31009
PEX10	NM_002617 /// NM_153818	-0.808955
PGK1	NM_000291	1.36181
PHACTR2	NM_014721	0.768814
PLAU	NM_002658	0.790224
PLEKHA1	NM_001001974 /// NM_021622	0.925551
PLOD2	NM_000935 /// NM_182943	-0.824097
PLSCR4	NM_020353	1.14232
PMCH	NM_002674	1.18614
POLR3G	NM_006467	-1.6809
PPAP2B	NM_003713 /// NM_177414	1.04907
PSMB9	NM_002800 /// NM_148954	0.73459
PTGER4	NM_000958	0.799802
PTK9	NM_002822 /// NM_198974	0.841813
PTPN12	NM_002835	1.13139
PTX3	NM_002852	0.958806
PXN	NM_002859	-0.779877
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.913473
RAB11FIP1	NM_001002233 /// NM_001002814 /// NM_025151	-1.11162
RAB2	NM_002865	1.08268
RAB21	NM_014999	-0.782285
RARRES1	NM_002888 /// NM_206963	0.703277
RCBTB2	NM_001268	1.24665
RDX	NM_002906	1.00725
RECK	NM_021111	1.34241
RGS2	NM_002923	1.12076
RHEB	NM_005614	1.01911

RHOQ	NM_012249	-1.43035
RHOQ /// LOC284988	NM_012249 /// XM_209429	-1.20819
RIP	NM_001033002 /// NM_032308	1.25909
ROR1	NM_005012	0.797888
RPL38	NM_000999	0.986019
RPS11	NM_001015	0.786637
RPS6KA5	NM_004755 /// NM_182398	0.783023
S100A2	NM_005978	1.10878
SC4MOL	NM_001017369 /// NM_006745	-2.06161
SCARB2	NM_005506	0.713034
SCG2	NM_003469	2.1007
SE57-1	NM_025214	-1.06691
SEMA3C	NM_006379	1.02281
SEPT6 /// N-PAC	NM_015129 /// NM_032569 /// NM_145799 /// NM_145800 /// NM_145802	0.938411
SEPT9	NM_006640	-0.701167
SERPINB9	NM_004155	1.0629
SERPINE2	NM_006216	0.728703
SH3GLB2	NM_020145	-0.822875
SHOX2	NM_003030 /// NM_006884	1.22331
SLC26A2	NM_000112	0.70957
SLC2A3	NM_006931	-1.3362
SLC2A3 /// SLC2A14	NM_006931 /// NM_153449	-0.931892
SLC33A1	NM_004733	-1.06356
SMA4	NM_021652	1.11134
SMARCA2	NM_003070 /// NM_139045	0.761273
SNAI2	NM_003068	1.08823
SNAP25	NM_003081 /// NM_130811	1.51132
SORBS3	NM_001018003 /// NM_005775	-0.796389
SPANXA1 /// SPANXB1 /// SPANXA2 /// SPANXC /// SPANXB2	NM_013453 /// NM_022661 /// NM_032461 /// NM_145662 /// NM_145664	1.53664
SPARC	NM_003118	1.19943
SPOCK	NM_004598	1.09606
SRD5A1	NM_001047	-1.13979
SRPX	NM_006307	1.1299
SSH1	NM_018984	1.02542
STC1	NM_003155	1.13679
STK39	NM_013233	-1.35492
SUMO2	NM_001005849 /// NM_006937	0.890434
SYNCRIP	NM_006372	1.25513
TAF15	NM_003487 /// NM_139215	0.956591
TAGLN	NM_001001522 /// NM_003186	1.32797
TCF4	NM_003199	1.09944
TCF8	NM_030751	0.704819
TGFBR3	NM_003243	1.50748
THBD	NM_000361	0.825199
TIMM17A	NM_006335	-1.14153
TNC	NM_002160	2.27045
TNFRSF9	NM_001561	1.08911
TPR	NM_003292	0.726403
TRA1	NM_003299	1.64234

TRAPPC4	NM_016146	-1.07164
TUBB4	NM_006087	-1.39921
TXN	NM_003329	1.07471
UGT1A8 /// UGT1A9	NM_019076 /// NM_021027	-1.1245
ULK1	NM_003565	-1.31566
UQCRB	NM_006294	-1.12095
VAV3	NM_006113	-0.951341
VDAC1	NM_003374	-0.976178
VDR	NM_000376 /// NM_001017535	1.09287
VEGFC	NM_005429	1.05478
WDR76	NM_024908	0.710363
XTP2	NM_015172	0.775788
YDD19	---	-1.14172
YDD19 /// C6orf68 /// LOC389850 /// LOC440128	NM_138459 /// XM_372205 /// XR_000254	-1.23685
ZNF259	NM_003904	-1.00795
ZNF551	NM_138347	0.884017
ZNF573	NM_152360	1.31557

Table 1C. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with anti-hsa-miR-31.

Gene Symbol	**RefSeq Transcript ID** (Pruitt et al., 2005)	**$\Delta \log_2$**
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	0.881687
ANPEP	NM_001150	0.773871
AXL	NM_001699 /// NM_021913	0.867317
BIRC3	NM_001165 /// NM_182962	0.736116
CXCL1	NM_001511	1.18869
CXCL2	NM_002089	1.1814
CXCL3	NM_002090	0.800224
CXCL5	NM_002994	0.844167
HIPK3	NM_005734	0.761797
IL6ST	NM_002184 /// NM_175767	0.85816
IL8	NM_000584	1.54253
LRP12	NM_013437	0.745576
MAFF	NM_012323 /// NM_152878	0.873461
NID1	NM_002508	0.818989
OPLAH	NM_017570	0.721461
PTGS2	NM_000963	0.832017
PTPN12	NM_002835	0.727176
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.773843
RDX	NM_002906	0.936655
SLC26A2	NM_000112	0.784073
SOD2	NM_000636 /// NM_001024465 /// NM_001024466	1.12431
SPTBN1	NM_003128 /// NM_178313	0.723649
STC1	NM_003155	0.904092
TNC	NM_002160	0.715844
TNFAIP3	NM_006290	0.788213

Table 1D. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-145.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	$\Delta \log_2$
AXL	NM_001699 /// NM_021913	0.775236939
CGI-48	NM_016001	0.771224792
CXCL3	NM_002090	0.742720639
IL8	NM_000584	0.769997216
LMO4	NM_006769	-0.715738257
NUCKS	NM_022731	0.763122861
PGK1	NM_000291	0.847051401
PMCH	NM_002674	0.865940473
RAB2	NM_002865	0.807863694
RDX	NM_002906	0.743529157
RPL38	NM_000999	0.739789501
TRA1	NM_003299	1.107966463
TXN	NM_003329	0.843252007

Table 1E. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-147.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	$\Delta \log_2$
ABCA1	NM_005502	-1.0705079
ALDH6A1	NM_005589	0.921996293
ANK3	NM_001149 /// NM_020987	1.175319831
ANKRD46	NM_198401	0.798089258
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	-1.290010791
ANXA10	NM_007193	-0.76954436
APOH	NM_000042	1.116058445
AQP3	NM_004925	1.293583496
ARG2	NM_001172	2.214496965
ARHGDIA	NM_004309	-0.71895894
ARID5B	NM_032199	1.249175823
ARL2BP	NM_012106	0.852981303
ARL7	NM_005737	-1.097275914
ARTS-1	NM_016442	-0.754098539
ATF5	NM_012068	-0.716057584
ATP6V0E	NM_003945	-0.84096275
ATP9A	NM_006045	0.752911182
AXL	NM_001699 /// NM_021913	0.793637153
B4GALT1	NM_001497	-0.776574082
BCL2A1	NM_004049	-2.000359314
BCL6	NM_001706 /// NM_138931	0.751950658
BICD2	NM_001003800 /// NM_015250	-0.818215213
BTG3	NM_006806	-1.374399564
BTN3A2	NM_007047	-1.06699734
C19orf2	NM_003796 /// NM_134447	-0.876512872
C1orf24	NM_022083 /// NM_052966	-0.78341048
C21orf25	NM_199050	-1.053798237
C2orf17	NM_024293	-1.039115573
C2orf31	---	0.791392536
C6orf120	NM_001029863	-0.832480385

CA12	NM_001218 /// NM_206925	-0.989153023
CA2	NM_000067	0.733866747
CASP7	NM_001227 /// NM_033338 /// NM_033339 /// NM_033340	-0.780385444
CCL2	NM_002982	-1.182060911
CCND1	NM_053056	-1.435105691
CCNG1	NM_004060 /// NM_199246	0.928408016
CDC37L1	NM_017913	-1.026820179
CDH4	NM_001794	-1.027487702
COBLL1	NM_014900	0.931189433
COL3A1	NM_000090	0.969777477
COL4A1	NM_001845	-1.178971961
COL4A2	NM_001846	-1.459851683
COQ2	NM_015697	-0.83915296
CRIPT	NM_014171	-1.110146535
CSNK1A1	NM_001025105 /// NM_001892	-0.717262814
CSPG2	NM_004385	-1.037433363
CTDSP2	NM_005730	1.103871011
CTH	NM_001902 /// NM_153742	1.482227168
CTSS	NM_004079	-0.704674455
CXCL5	NM_002994	0.758779818
DAZAP2	NM_014764	-1.232967024
DAZAP2 /// LOC401029	NM_014764 /// XM_376165	-0.876163094
DCBLD2	NM_080927	-0.813731475
DCP2	NM_152624	1.187108067
DDAH1	NM_012137	1.133236922
DHCR24	NM_014762	0.962804049
DIO2	NM_000793 /// NM_001007023 /// NM_013989	-0.809284862
DKFZP586A0522	NM_014033	0.957989488
DNAJB6	NM_005494 /// NM_058246	-1.120505456
DNAJC15	NM_013238	1.186534996
DOCK4	NM_014705	-0.824536256
DPYSL4	NM_006426	0.800773508
DSC2	NM_004949 /// NM_024422	1.11600402
DST	NM_001723 /// NM_015548 /// NM_020388 /// NM_183380	1.317689575
DUSP1	NM_004417	-1.036787804
EIF2C1	NM_012199	-0.849818302
EIF2S1	NM_004094	-1.211812274
EIF5A2	NM_020390	-0.703223281
EPHB2	NM_004442 /// NM_017449	-1.171343772
EREG	NM_001432	-1.346940189
ETS2	NM_005239	-0.783135629
F2RL1	NM_005242	-0.861042737
FAM18B	NM_016078	-0.768704947
FAM45B /// FAM45A	NM_018472 /// NM_207009	-0.905122961
FAM46A	NM_017633	1.189436349
FGB	NM_005141	1.133519364
FGFR3	NM_000142 /// NM_022965	1.175488465
FGFR4	NM_002011 /// NM_022963 /// NM_213647	0.778320037

FGG	NM_000509 /// NM_021870	1.161946748
FGL1	NM_004467 /// NM_147203 /// NM_201552 /// NM_201553	0.920382947
FJX1	NM_014344	-1.631423993
FLJ13910	NM_022780	0.874893502
FLJ21159	NM_024826	-0.836849616
FLJ31568	NM_152509	1.050523485
FLRT3	NM_013281 /// NM_198391	1.084587332
FOSL1	NM_005438	-1.004370563
FTS	NM_001012398 /// NM_022476	-1.105648276
FYCO1	NM_024513	-1.849492859
FZD7	NM_003507	0.730854769
G1P2	NM_005101	-1.070255287
GABRA5	NM_000810	-1.370874696
GATA6	NM_005257	1.250224603
GK	NM_000167 /// NM_203391	0.823046538
GLI2	NM_005270 /// NM_030379 /// NM_030380 /// NM_030381	-0.770685407
GLIPR1	NM_006851	-1.047885319
GLUL	NM_001033044 /// NM_001033056 /// NM_002065	0.889617404
GNS	NM_002076	-1.07857689
GOLPH2	NM_016548 /// NM_177937	-0.926612282
GYG2	NM_003918	0.975758283
HAS2	NM_005328	-1.136601383
HCCS	NM_005333	-1.169843196
HIC2	NM_015094	1.040798749
HKDC1	NM_025130	-0.742677043
HMGCS1	NM_002130	0.710761737
HN1	NM_001002032 /// NM_001002033 /// NM_016185	-1.288713253
ID4	NM_001546	1.050108032
IDS	NM_000202 /// NM_006123	-0.765358291
IGFBP1	NM_000596 /// NM_001013029	-1.279099713
IGFBP4	NM_001552	-0.739326913
IL11	NM_000641	-2.089747129
IL15	NM_000585 /// NM_172174 /// NM_172175	-0.854711689
IL8	NM_000584	-1.711808874
IQGAP2	NM_006633	0.913042194
ITGB4	NM_000213 /// NM_001005619 /// NM_001005731	-1.186739806
JAK1	NM_002227	-1.059987123
JUN	NM_002228	-0.846308702
KCNMA1	NM_001014797 /// NM_002247	-1.281096095
KCNS3	NM_002252	0.763898782
KIAA0494	NM_014774	-1.372898343
KIAA0882	NM_015130	-0.980703295
KLF10	NM_001032282 /// NM_005655	-1.116428
KRT4	NM_002272	1.064537576
LEPROT	NM_017526	-1.018363603
LHFP	NM_005780	-1.0271939
LIMK1	NM_002314 /// NM_016735	-1.803777658
LRP12	NM_013437	-0.743603255

LRRC54	NM_015516	-0.77656268
M6PR	NM_002355	-1.386148277
MAP3K1	XM_042066	0.759959443
MAP3K2	NM_006609	-1.363559174
MARCH6	NM_005885	-1.202139411
MATN3	NM_002381	0.903494673
MGAM	NM_004668	1.167350858
MGC11332	NM_032718	-1.007976707
MICA	NM_000247	-1.41026822
MICAL2	NM_014632	-0.823900817
MOBK1B	NM_018221	-1.127633961
NAGK	NM_017567	-1.06761962
NAV3	NM_014903	-0.701500848
NES	NM_006617	0.824166211
NID1	NM_002508	0.712358426
NPAS2	NM_002518	-1.314671396
NPTX1	NM_002522	-1.366083158
NUPL1	NM_001008564 /// NM_001008565 /// NM_014089	-0.927879559
OBSL1	XM_051017	1.078419022
OLFML3	NM_020190	-0.772616072
OLR1	NM_002543	0.783582212
OSTM1	NM_014028	-1.349848003
OXTR	NM_000916	-1.248290182
P8	NM_012385	1.102960353
PDCD4	NM_014456 /// NM_145341	0.732196292
PDZK1	NM_002614	1.13249347
PDZK1IP1	NM_005764	-0.764992528
PELI2	NM_021255	1.052234224
PFKP	NM_002627	-1.304130926
PKP2	NM_001005242 /// NM_004572	0.957319593
PLAU	NM_002658	-1.546762739
POLR3G	NM_006467	-1.758348197
PON2	NM_000305 /// NM_001018161	-0.891886921
PSMB9	NM_002800 /// NM_148954	-0.764503658
PTHLH	NM_002820 /// NM_198964 /// NM_198965 /// NM_198966	-0.85479181
RAB11FIP1	NM_001002233 /// NM_001002814 /// NM_025151	-0.710783895
RAB22A	NM_020673	-1.287081241
RARRES1	NM_002888 /// NM_206963	0.766334915
RBKS	NM_022128	-1.116205272
RGC32	NM_014059	0.956745628
RHOC	NM_175744	-1.073877719
RNH1	NM_002939 /// NM_203383 /// NM_203384 /// NM_203385 /// NM_203386 /// NM_203387	-1.119287238
RRM2	NM_001034	-1.047471119
S100P	NM_005980	1.564388795
SERF1A /// SERF1B	NM_021967 /// NM_022978	-1.00166157
SERPINE1	NM_000602	-2.401636366
SGPL1	NM_003901	-0.977828602

SKP2	NM_005983 /// NM_032637	0.7230064
SLC26A2	NM_000112	-0.804718831
SPANXA1 /// SPANXB1 /// SPANXA2 /// SPANXC /// SPANXB2	NM_013453 /// NM_022661 /// NM_032461 /// NM_145662 /// NM_145664	0.723441371
SPARC	NM_003118	1.275598165
SPOCK	NM_004598	-1.416025909
STC1	NM_003155	-1.031822774
STX3A	NM_004177	0.738540782
SYNE1	NM_015293 /// NM_033071 /// NM_133650 /// NM_182961	-0.986137779
TBC1D2	NM_018421	-1.036883659
TGFBR2	NM_001024847 /// NM_003242	-1.121957889
TJP2	NM_004817 /// NM_201629	1.028659136
TM4SF20	NM_024795	0.857516073
TM4SF4	NM_004617	-0.844385261
TM7SF1	NM_003272	-1.650275939
TMC5	NM_024780	-0.810437274
TMEPAI	NM_020182 /// NM_199169 /// NM_199170 /// NM_199171	-1.096653239
TNFAIP6	NM_007115	-1.865722451
TNFRSF12A	NM_016639	-0.842444428
TNRC9	XM_049037	0.870669505
TSPAN8	NM_004616	0.735887176
TXLNA	NM_175852	-0.882047143
UEV3	NM_018314	-1.113012978
ULK1	NM_003565	-0.728593583
USP46	NM_022832	-1.598797937
VANGL1	NM_138959	-1.036428715
VDR	NM_000376 /// NM_001017535	-0.744474059
VLDLR	NM_001018056 /// NM_003383	-1.105779636
VTN	NM_000638	0.969767951
WBSCR22	NM_017528	-0.703785254
ZBTB10	NM_023929	0.853410353
ZNF467	NM_207336	1.07813993

Table 1F. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-188.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**$\Delta \log_2$**
15E1.2	NM_176818	-1.141638876
ADARB1	NM_001033049 /// NM_001112 /// NM_015833 /// NM_015834	0.744410733
AER61	NM_173654	-0.899131245
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	-0.941957418
ANKFY1	NM_016376 /// NM_020740	0.668007407
ANKRD46	NM_198401	0.834094665
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	0.757775366
AR	NM_000044 /// NM_001011645	-0.805079746
AREG	NM_001657	0.604163284

ARL2BP	NM_012106	0.797577768
ATP2B4	NM_001001396 /// NM_001684	-1.153875577
ATP6V0E	NM_003945	1.113609299
ATXN1	NM_000332	-1.225362507
AXL	NM_001699 /// NM_021913	0.741305367
B3GNT6	NM_006876	0.609445079
B4GALT1	NM_001497	-0.787396891
B4GALT4	NM_003778 /// NM_212543	-0.797950275
BAMBI	NM_012342	-0.832397669
BCL6	NM_001706 /// NM_138931	-0.807800523
BPGM	NM_001724 /// NM_199186	-1.729772661
C3	NM_000064	0.776240618
C6orf120	NM_001029863	-1.427214532
C8orf1	NM_004337	-0.783453122
C9orf116	NM_144654	0.657870647
CACNA1G	NM_018896 /// NM_198376 /// NM_198377 /// NM_198378 /// NM_198379 /// NM_198380	-0.707185799
CAP1	NM_006367	-1.13643337
CBFB	NM_001755 /// NM_022845	-1.261357593
CCDC6	NM_005436	-1.009649239
CCNA2	NM_001237	-0.791748727
CD2AP	NM_012120	-1.121212839
CDH1	NM_004360	-0.977612615
CDK2AP1	NM_004642	-1.537435476
CGI-48	NM_016001	1.035693465
CLU	NM_001831 /// NM_203339	-1.205042129
CMAS	NM_018686	0.608108313
COL1A1	NM_000088	-1.058828289
COL6A1	NM_001848	0.735178781
CREB3L2	NM_194071	-1.092835167
CSNK1A1	NM_001025105 /// NM_001892	-1.183929257
CSPG2	NM_004385	-0.850672076
CXCL1	NM_001511	0.876432556
CXCL2	NM_002089	0.797235609
CXCL3	NM_002090	0.633880719
DAAM1	NM_014992	-0.859090846
DCP2	NM_152624	0.972517476
DDAH1	NM_012137	0.885174702
DDX3Y	NM_004660	0.609355038
DHRS2	NM_005794 /// NM_182908	1.085977439
DICER1	NM_030621 /// NM_177438	0.653180698
DIO2	NM_000793 /// NM_001007023 /// NM_013989	0.979459766
DKFZp564K142	NM_032121	-1.413051709
DLG5	NM_004747	-1.157557972
EDEM1	NM_014674	-1.180379773
EEF1D	NM_001960 /// NM_032378	0.614858402
EIF2S1	NM_004094	-1.263958652
ELF3	NM_004433	-1.133314137
ELOVL6	NM_024090	-0.722875346
EMP1	NM_001423	-0.83814704
ENPP4	NM_014936	0.744738095

ETS2	NM_005239	-1.020837722
FAM18B	NM_016078	-0.717468957
FAS	NM_000043 /// NM_152871 /// NM_152872 /// NM_152873 /// NM_152874 /// NM_152875	0.692619708
FBXO11	NM_012167 /// NM_018693 /// NM_025133	0.625568603
FEM1B	NM_015322	-1.158919916
FGF2	NM_002006	-0.843439627
FGFBP1	NM_005130	0.614373013
FGG	NM_000509 /// NM_021870	-0.763121708
FLJ13910	NM_022780	0.818728904
FN5	NM_020179	-1.270232536
GABRA5	NM_000810	0.772270023
GATAD1	NM_021167	-1.295620295
GPR125	NM_145290	-1.243715655
GREM1	NM_013372	-1.068628761
H2AFY	NM_004893 /// NM_138609 /// NM_138610	-0.93507394
HDAC3	NM_003883	-0.73639501
HIPK3	NM_005734	0.892438313
HMOX1	NM_002133	0.628367832
HNRPA0	NM_006805	-1.164494165
IDS	NM_000202 /// NM_006123	-1.270124871
IER3IP1	NM_016097	0.707420006
IGFBP3	NM_000598 /// NM_001013398	0.707305602
IL11	NM_000641	-1.199790518
IL13RA1	NM_001560	-1.079298214
IL6ST	NM_002184 /// NM_175767	-1.000365688
IL8	NM_000584	1.192438588
INHBC	NM_005538	0.947119793
ITGAV	NM_002210	-0.830296216
KCNJ2	NM_000891	0.756259837
KLF4	NM_004235	-1.094778613
LGALS8	NM_006499 /// NM_201543 /// NM_201544 /// NM_201545	-1.161162739
LOC348162	XM_496132	-0.754126245
LOC389435	XM_371853	0.79767725
LOC440118	XM_498554	1.068888477
LOC492304	NM_001007139	-0.993171411
LZTFL1	NM_020347	1.067917522
M6PR	NM_002355	-0.702214209
MAP4K5	NM_006575 /// NM_198794	-1.315004609
MARCKS	NM_002356	-1.719459875
MCL1	NM_021960 /// NM_182763	0.851818869
MNS1	NM_018365	0.610385691
MYBL1	XM_034274	0.642317846
NEFL	NM_006158	0.894724681
NPC1	NM_000271	0.66862526
NUCKS	NM_022731	0.809644166
OBSL1	XM_051017	0.624763532
PALM2-AKAP2	NM_007203 /// NM_147150	-0.952675045
PCAF	NM_003884	-0.884319067

PCTP	NM_021213	-1.860357999
PDZK1IP1	NM_005764	0.814065246
PER2	NM_003894 /// NM_022817	-0.820618961
PGK1	NM_000291	1.458841167
PHACTR2	NM_014721	-0.994794647
PLEKHA1	NM_001001974 /// NM_021622	-1.087541297
PMCH	NM_002674	0.891819035
PPAP2B	NM_003713 /// NM_177414	1.09654097
PRKCA	NM_002737	-0.74986976
PRO1843	---	0.637923257
PTEN	NM_000314	-1.18340148
RAB2	NM_002865	0.618790048
RAB22A	NM_020673	-0.857364776
RASSF3	NM_178169	-1.056858481
RBL1	NM_002895 /// NM_183404	-1.832181472
RDX	NM_002906	0.671620551
RGS20	NM_003702 /// NM_170587	-1.031805989
RHEB	NM_005614	1.046807861
RIP	NM_001033002 /// NM_032308	1.002233258
RNASE4	NM_002937 /// NM_194430 /// NM_194431	-1.041252911
RPL14	NM_001034996 /// NM_003973	0.675935571
RPL38	NM_000999	1.018133464
RPS11	NM_001015	0.711318114
RRAGD	NM_021244	1.032780698
RSAD1	NM_018346	-1.158852158
SDC4	NM_002999	-0.827651439
SEMA3C	NM_006379	0.728585504
SESN1	NM_014454	0.673607805
SFRS7	NM_001031684 /// NM_006276	-1.839856588
SLC39A9	NM_018375	-1.641258804
SLC4A4	NM_003759	-0.735121994
SNAP25	NM_003081 /// NM_130811	0.867961925
SOCS2	NM_003877	0.794942635
SOX18	NM_018419	2.106732425
ST13	NM_003932	-1.524583796
ST7	NM_018412 /// NM_021908	0.63130334
STC1	NM_003155	0.734717673
SUMO2	NM_001005849 /// NM_006937	0.655067952
SYNJ2BP	NM_018373	-1.080440275
TAPBP	NM_003190 /// NM_172208 /// NM_172209	-1.960164768
TBL1X	NM_005647	-0.868396691
TGFBR3	NM_003243	0.661346605
TM4SF4	NM_004617	1.144720409
TMBIM1	NM_022152	-1.287361343
TNRC9	XM_049037	-0.771759846
TOX	NM_014729	0.758056848
TP73L	NM_003722	-1.07919526
TRA1	NM_003299	1.168505036
TRPC1	NM_003304	-1.27624829
TXN	NM_003329	1.396905762
VAPB	NM_004738	-1.101210395

VAV3	NM_006113	-1.259645983
VDAC3	NM_005662	0.618698521
WDR39	NM_004804	-1.124206635
WDR41	NM_018268	-0.858885381
WISP2	NM_003881	1.240802507
WSB2	NM_018639	0.725624688
ZNF281	NM_012482	-1.086219759

Table 1G. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-215.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**$\Delta \log_2$**
15E1.2	NM_176818	0.205437058
AADAC	NM_001086	0.613615652
AASDHPPT	NM_015423	-1.494197703
ABAT	NM_000663 /// NM_020686	0.321959311
ABCA1	NM_005502	0.699750598
ABCC1	NM_004996 /// NM_019862 /// NM_019898 /// NM_019899 /// NM_019900 /// NM_019901	0.127920178
ABHD3	NM_138340	0.854113684
ABLIM3	NM_014945	0.952575867
ACADSB	NM_001609	-1.055415881
ACTR2	NM_001005386 /// NM_005722	0.141687247
ADARB1	NM_001033049 /// NM_001112 /// NM_015833 /// NM_015834	0.145448262
ADCY7	NM_001114	-1.016445175
ADRB2	NM_000024	1.151729447
AER61	NM_173654	-0.750205603
AIP	NM_003977	0.070101115
AKAP12	NM_005100 /// NM_144497	0.070257378
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	0.998820355
ALDH6A1	NM_005589	0.081889528
ANG /// RNASE4	NM_001145 /// NM_002937 /// NM_194430 /// NM_194431	-0.789162296
ANK3	NM_001149 /// NM_020987	0.073849016
ANKFY1	NM_016376 /// NM_020740	0.407103029
ANKRD12	NM_015208	0.83611804
ANKRD46	NM_198401	0.253728454
ANPEP	NM_001150	0.43537024
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	-0.989899193
ANXA10	NM_007193	0.207283719
AOX1	NM_001159	1.057940273
AP3D1	NM_003938	0.289422815
APBA2BP	NM_031231 /// NM_031232	0.092824985
APBB2	NM_173075	0.148967006
APOL1	NM_003661 /// NM_145343 /// NM_145344	0.430559196
APOL2	NM_030882 /// NM_145637	0.406585331
APOL6	NM_030641	0.284258575
APP	NM_000484 /// NM_201413 /// NM_201414	1.032937045

APPBP2	NM_006380	0.303015566
AQP3	NM_004925	-1.164146946
AREG	NM_001657	0.211309877
ARF7	NM_025047	1.114359532
ARG2	NM_001172	0.086547513
ARHGAP11A	NM_014783 /// NM_199357	-1.073287033
ARHGAP29	NM_004815	-1.569413849
ARHGAP8 /// LOC553158	NM_001017526 /// NM_181334 /// NM_181335	0.325649614
ARHGDIB	NM_001175	0.585266905
ARL2	NM_001667	0.119082943
ARL2BP	NM_012106	0.786926841
ARTS-1	NM_016442	0.852001464
ASMTL	NM_004192	0.309606772
ATP2B4	NM_001001396 /// NM_001684	0.723181241
ATP6V0E	NM_003945	1.51677341
ATP6V1A	NM_001690	0.295502657
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ATRX	NM_000489 /// NM_138270 /// NM_138271	0.347353063
AVPI1	NM_021732	0.345999149
AXL	NM_001699 /// NM_021913	0.20482975
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B4GALT1	NM_001497	0.354652953
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BIRC3	NM_001165 /// NM_182962	0.130792426
BNC2	NM_017637	0.402525944
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BUB1	NM_004336	-0.827828304
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C14orf87	NM_016417	0.124434236
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C1R	NM_001733	0.509802443
C21orf25	NM_199050	0.786708643
C2orf25	NM_015702	0.26479972
C3	NM_000064	0.827896244
C4BPB	NM_000716 /// NM_001017364 /// NM_001017365 ///NM_001017366 /// NM_001017367	0.62576874
C5orf13	NM_004772	0.125660919
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C6orf120	NM_001029863	0.434310918
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C8orf1	NM_004337	0.562915913
C9orf9	NM_018956	0.130263432
C9orf95	NM_017881	1.031138782
CA8	NM_004056	0.254013695
CACNA1G	NM_018896 /// NM_198376 /// NM_198377 /// NM_198378 /// NM_198379 /// NM_198380	0.457971451
CALB2	NM_001740 /// NM_007087 /// NM_007088	1.14387436
CAP2	NM_006366	0.159109138
CAP350	NM_014810	0.268617251
CASP2	NM_001224 /// NM_032982 /// NM_032983	0.152714052
CBFB	NM_001755 /// NM_022845	-1.091964495
CCDC28A	NM_015439	0.095731564
CCL20	NM_004591	0.181602375
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CCNG1	NM_004060 /// NM_199246	1.083676653
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CD38	NM_001775	-0.830682734
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CD9	NM_001769	0.17073077
CDC14B	NM_003671 /// NM_033331 /// NM_033332	0.186021553
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CDC42BPA	NM_003607 /// NM_014826	0.260390886
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CDCP1	NM_022842 /// NM_178181	0.406951554
CDH1	NM_004360	-0.718140698
CDH17	NM_004063	0.273335963
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CDR2	NM_001802	0.071008893
CEACAM1	NM_001024912 /// NM_001712	0.365461154
CEACAM6	NM_002483	0.664522916
CFLAR	NM_003879	0.359551649
CGI-48	NM_016001	1.375743217
CHAF1A	NM_005483	-0.810171421
CHMP5	NM_016410	0.230410536
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COL5A1	NM_000093	0.139512165
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COMMD8	NM_017845	0.259087589
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COPS7A	NM_016319	-1.253849195
CPM	NM_001005502 /// NM_001874 /// NM_198320	0.304563812
CPNE1	NM_003915 /// NM_152925 /// NM_152926/// NM_152927 /// NM_152928 /// NM_152929	-1.009304194
CPS1	NM_001875	-1.3665196
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CRTAP	NM_006371	0.124549981
CSF2RA	NM_006140 /// NM_172245 /// NM_172246 /// NM_172247 /// NM_172248 /// NM_172249	0.629927794
CSPG6	NM_005445	0.349486373
CTAGE5	NM_005930 /// NM_203354 /// NM_203355 /// NM_203356 /// NM_203357	0.841770238
CTDSP2	NM_005730	0.471052412
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CTSS	NM_004079	0.943772117
CXCR4	NM_001008540 /// NM_003467	0.105713361
CYorf15B	NM_032576	0.463405313
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DEAF1	NM_021008	-1.007418894
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DMN	NM_015286 /// NM_145728	-0.821232265
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EHF	NM_012153	0.790943966
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EPAS1	NM_001430	0.623440449
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HBXIP	NM_006402	-1.154923271
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HGD	NM_000187	0.173420553
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HMGA2	NM_001015886 /// NM_003483 /// NM_003484	0.564944378
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IFIT1	NM_001001887 /// NM_001548	0.379643177
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IRF1	NM_002198	0.306448619
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ITGA2	NM_002203	0.342710638
ITGAM	NM_000632	0.268719412
ITGB4	NM_000213 /// NM_001005619 /// NM_001005731	0.155043366
ITPR2	NM_002223	0.09186773
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PDZK1	NM_002614	0.447912028
PDZK1IP1	NM_005764	0.433988406
PEG10	XM_496907 /// XM_499343	-0.850603677
PFAAP5	NM_014887	1.00995749
PFKP	NM_002627	0.145073784
PGK1	NM_000291	1.653917029
PHTF2	NM_020432	-1.435962859
PIAS1	NM_016166	0.329831807
PICALM	NM_001008660 /// NM_007166	0.542347896
PIK3CD	NM_005026	0.127328669
PIP5K2B	NM_003559 /// NM_138687	-1.176282316
PIR	NM_001018109 /// NM_003662	0.160554881
PKP2	NM_001005242 /// NM_004572	0.155908373

PKP3	NM_007183	0.111221571
PLA1A	NM_015900	0.519309601
PLAT	NM_000930 /// NM_000931 /// NM_033011	0.146078428
PLAU	NM_002658	-0.824554099
PLCB1	NM_015192 /// NM_182734	0.155103034
PLD3	NM_001031696 /// NM_012268	0.210088214
PLEC1	NM_000445 /// NM_201378 /// NM_201379 /// NM_201380 /// NM_201381 /// NM_201382	0.33673122
PLEKHA1	NM_001001974 /// NM_021622	0.131973111
PLEKHC1	NM_006832	0.584776549
PLK2	NM_006622	0.326572118
PLSCR4	NM_020353	0.46221002
PMAIP1	NM_021127	0.491091157
PMCH	NM_002674	0.871730513
PMM1	NM_002676	0.216617697
PNMA2	NM_007257	0.139625087
PODXL	NM_001018111 /// NM_005397	0.456394836
POLR3D	NM_001722	0.08207198
PPAP2B	NM_003713 /// NM_177414	0.297210716
PPIF	NM_005729	0.339361634
PPL	NM_002705	0.486464001
PPM1D	NM_003620	0.270391658
PPM1H	XM_350880	-1.013741351
PPP1CA	NM_001008709 /// NM_002708 /// NM_206873	-1.894131186
PPP1CB	NM_002709 /// NM_206876 /// NM_206877	-1.783955222
PPP1R12A	NM_002480	-1.084874225
PPP1R15A	NM_014330	0.100377423
PPP3CB	NM_021132	0.206923376
PREI3	NM_015387 /// NM_199482	0.071987049
PRG1	NM_002727	0.331289574
PRKAG2	NM_016203	0.385982127
PRNP	NM_000311 /// NM_183079	-0.958358216
PRO1843	---	1.041783261
PROSC	NM_007198	0.106952242
PSD3	NM_015310 /// NM_206909	0.410750005
PSMB8	NM_004159 /// NM_148919	0.407217056
PSMB9	NM_002800 /// NM_148954	0.174187504
PSMD6	NM_014814	-1.13875629
PSME4	NM_014614	0.608592775
PTEN	NM_000314	0.077948271
PTENP1	---	0.854304606
PTER	NM_001001484 /// NM_030664	0.197797186
PTGES	NM_004878 /// NM_198797	0.472784339
PTGS2	NM_000963	-1.166655131
PTK9	NM_002822 /// NM_198974	0.27994916
PTPN12	NM_002835	0.98401718
PTS	NM_000317	-1.077350104
PYCARD	NM_013258 /// NM_145182 /// NM_145183	0.334732997

QDPR	NM_000320	0.117706826
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.104561101
RAB2	NM_002865	-1.472842476
RAB21	NM_014999	0.173725538
RAB22A	NM_020673	0.144802244
RAB40B	NM_006822	-0.724439401
RARRES1	NM_002888 /// NM_206963	-0.872731167
RARRES3	NM_004585	0.937698042
RASGRP1	NM_005739	0.283283996
RASSF2	NM_014737 /// NM_170773 /// NM_170774	0.073730084
RB1	NM_000321	-1.019393484
RBKS	NM_022128	0.284148207
RBM35A	NM_001034915 /// NM_017697	0.265540631
RBP4	NM_006744	-1.206604909
RDX	NM_002906	0.128180803
RECK	NM_021111	0.606071832
RGS2	NM_002923	0.459812167
RGS20	NM_003702 /// NM_170587	0.105813927
RHEB	NM_005614	1.24347853
RHOB	NM_004040	0.867434204
RHOC	NM_175744	0.128155822
RIG	---	0.494706599
RIP	NM_001033002 /// NM_032308	1.275556601
RIPX	NM_014961	0.213459642
RIT1	NM_006912	0.274644355
RNF141	NM_016422	-0.805841944
RP2	NM_006915	0.833754103
RPE	NM_006916 /// NM_199229	-0.862237229
RPE /// LOC440001	NM_006916 /// NM_199229 /// XM_495848	-0.882376602
RPL14	NM_001034996 /// NM_003973	0.951492657
RPL38	NM_000999	1.594089757
RPL4	NM_000968	-1.286483789
RPS11	NM_001015	1.344642602
RPS6KA5	NM_004755 /// NM_182398	0.675214463
RRAGC	NM_022157	0.841252149
RRBP1	NM_004587	0.081532271
RSAD1	NM_018346	0.185020934
RTCD1	NM_003729	0.372814311
S100A2	NM_005978	0.287813299
S100P	NM_005980	0.42530058
SAMD4	NM_015589	0.429114508
SCAP2	NM_003930	0.150273464
SCARB2	NM_005506	0.343430868
SCEL	NM_003843 /// NM_144777	0.274457889
SCG2	NM_003469	0.242456207
SCML1	NM_006746	0.188454102
SCYL3	NM_020423 /// NM_181093	0.359002315
SDC1	NM_001006946 /// NM_002997	0.148749448
SEMA3C	NM_006379	0.315652462
SERPINB9	NM_004155	0.238442542

SERPINE1	NM_000602	-0.906971559
SERPINE2	NM_006216	0.690466045
SESN1	NM_014454	0.969021079
SF3B1	NM_001005526 /// NM_012433	0.270873508
SFRP4	NM_003014	-0.839989487
SGSH	NM_000199	0.105020333
SH3YL1	NM_015677	0.118050717
SIRT1	NM_012238	-0.95785137
SKP2	NM_005983 /// NM_032637	0.445430923
SLC19A2	NM_006996	-1.425040844
SLC1A4	NM_003038	-1.046830827
SLC26A2	NM_000112	-0.789593004
SLC2A3	NM_006931	0.741688417
SLC2A3 /// SLC2A14	NM_006931 /// NM_153449	0.777277784
SLC30A1	NM_021194	0.134188966
SLC35D1	NM_015139	0.168681771
SLC39A6	NM_012319	-0.991063322
SLC39A9	NM_018375	-0.845810525
SLC3A2	NM_001012661 /// NM_001012662 /// NM_001012663 /// NM_001012664 /// NM_001013251	-0.760455682
SLC6A6	NM_003043	0.62054439
SLC7A5	NM_003486	-0.805655634
SLCO2B1	NM_007256	0.544659891
SMA4	NM_021652	1.751441623
SMAD3	NM_005902	0.086804033
SMARCA2	NM_003070 /// NM_139045	0.693604829
SMG1	NM_015092	0.215996837
SMURF2	NM_022739	0.642895096
SNAI2	NM_003068	0.555123173
SNAP23	NM_003825 /// NM_130798	0.399400623
SNAP25	NM_003081 /// NM_130811	-1.144869946
SNRPD1	NM_006938	-1.238252269
SNX13	NM_015132	-1.077547837
SOAT1	NM_003101	-1.4130946
SOCS2	NM_003877	0.323697921
SOD2	NM_000636 /// NM_001024465 /// NM_001024466	0.191425651
SON	NM_003103 /// NM_032195 /// NM_058183 /// NM_138925 /// NM_138926 /// NM_138927	0.075763826
SOX18	NM_018419	2.548865238
SPANXA1 /// SPANXB1 /// SPANXA2 /// SPANXC /// SPANXB2	NM_013453 /// NM_022661 /// NM_032461 /// NM_145662 /// NM_145664	0.60551083
SPARC	NM_003118	0.701774899
SPEN	NM_015001	0.369917038
SPOCK	NM_004598	0.633114692
SPRY4	NM_030964	0.124707436
SPTBN1	NM_003128 /// NM_178313	0.596762123
SQRDL	NM_021199	0.139305673
SRD5A1	NM_001047	-0.797620547
SRI	NM_003130 /// NM_198901	0.196754507

SRP68	NM_014230	0.399780137
SS18	NM_001007559 /// NM_005637	-0.748405362
SSH1	NM_018984	0.523644692
ST7	NM_018412 /// NM_021908	0.1561475
STC1	NM_003155	0.297703216
STC2	NM_003714	0.508279396
STK24	NM_001032296 /// NM_003576	0.152558116
STX3A	NM_004177	0.847465024
STYK1	NM_018423	0.155415177
SULT1C1	NM_001056 /// NM_176825	0.292703007
SUMO2	NM_001005849 /// NM_006937	0.824463508
SVIL	NM_003174 /// NM_021738	0.59966071
SYDE1	NM_033025	0.1208585
SYNE1	NM_015293 /// NM_033071 /// NM_133650 /// NM_182961	0.245206316
SYNJ2BP	NM_018373	0.271987192
SYT1	NM_005639	0.558294006
TAF11	NM_005643	0.432194913
TAF15	NM_003487 /// NM_139215	1.023517036
TANK	NM_004180 /// NM_133484	0.381315138
TAPBP	NM_003190 /// NM_172208 /// NM_172209	0.213736434
TAPBPL	NM_018009	0.448113947
TARDBP	NM_007375	-0.757464386
TBC1D16	NM_019020	-1.153829054
TBC1D2	NM_018421	0.170439
TBL1X	NM_005647	-1.08552769
TBXAS1	NM_001061 /// NM_030984	0.237276142
TCF8	NM_030751	0.091754954
TDG	NM_001008411 /// NM_003211	1.007246808
TDO2	NM_005651	1.231162585
TFG	NM_001007565 /// NM_006070	0.864211334
TGFBR2	NM_001024847 /// NM_003242	0.718443392
TGFBR3	NM_003243	1.353282976
THBD	NM_000361	1.050136118
THUMPD1	NM_017736	0.255438593
TIPRL	NM_001031800 /// NM_152902	0.13795107
TLR3	NM_003265	0.419663385
TM4SF20	NM_024795	-1.548256638
TM7SF1	NM_003272	0.10894436
TMBIM1	NM_022152	0.135490816
TMC5	NM_024780	0.358722565
TMEM45A	NM_018004	-1.349843947
TMOD1	NM_003275	0.391840787
TNC	NM_002160	0.34702722
TncRNA	---	1.647849806
TNFAIP3	NM_006290	0.321123793
TNFRSF10B	NM_003842 /// NM_147187	0.537433829
TNFRSF12A	NM_016639	0.210104264
TNFRSF9	NM_001561	0.367983138
TNFSF9	NM_003811	1.103380988
TNS1	NM_022648	0.147994079
TOP1	NM_003286	0.220287943

TOR1AIP1	NM_015602	-2.805037892
TOX	NM_014729	0.928096328
TP53I3	NM_004881 /// NM_147184	0.434272014
TPD52	NM_001025252 /// NM_001025253 /// NM_005079	-0.860388426
TPR	NM_003292	0.674066928
TRA1	NM_003299	1.978956869
TRIM22	NM_006074	0.78338348
TRIM23	NM_001656 /// NM_033227 /// NM_033228	-0.762495255
TRIM8	NM_030912	0.355855943
TRIO	NM_007118	0.431960669
TRIOBP	NM_007032 /// NM_138632	0.402695141
TRIP13	NM_004237	-1.331218004
TSC	NM_017899	-0.770711093
TSPAN7	NM_004615	0.273204209
TTC10	NM_006531 /// NM_175605	0.099518838
TTC3	NM_001001894 /// NM_003316	0.491167754
TTC9	XM_027236	0.095337814
TTMP	NM_024616	-0.733612685
TUBB-PARALOG	NM_178012	-0.940699781
TXN	NM_003329	1.502649699
UBE2H	NM_003344 /// NM_182697	0.587860302
UBE2I	NM_003345 /// NM_194259 /// NM_194260 /// NM_194261	0.518745272
UBE2L6	NM_004223 /// NM_198183	0.353342853
UBE2V1 /// Kua-UEV	NM_001032288 /// NM_003349 /// NM_021988 /// NM_022442 /// NM_199144 /// NM_1992	0.277629969
UBTF	NM_014233	-0.732165826
UGCG	NM_003358	0.124116343
UGT1A8 /// UGT1A9	NM_019076 /// NM_021027	0.342387428
UQCRB	NM_006294	0.442020436
USP3	NM_006537	0.785643243
USP46	NM_022832	-1.013275727
VAMP8	NM_003761	0.554524584
VDAC3	NM_005662	1.1884143
VEZATIN	NM_017599	1.049647153
VIL2	NM_003379	0.184178997
VPS28	NM_016208 /// NM_183057	0.177114303
VTN	NM_000638	0.162694278
WIG1	NM_022470 /// NM_152240	-1.303047287
WIPI49	NM_017983	0.321050391
WISP2	NM_003881	0.224944436
WSB2	NM_018639	0.898521363
XTP2	NM_015172	1.647838848
YOD1	NM_018566	0.302211851
ZBED2	NM_024508	1.160901101
ZBTB10	NM_023929	-0.946044115
ZFHX1B	NM_014795	-0.71121339
ZNF198	NM_003453 /// NM_197968	0.154739368
ZNF22	NM_006963	0.186946885
ZNF551	NM_138347	0.119349113

ZNF573	NM_152360	0.388271249
ZNF609	NM_015042	1.118504396

Table 1H. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-216.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	$\Delta \log_2$
ANKRD46	NM_198401	1.205064294
ANPEP	NM_001150	1.05249117
ANTXR1	NM_018153 /// NM_032208 /// NM_053034	1.46843778
ARID5B	NM_032199	0.844356546
ATP2B4	NM_001001396 /// NM_001684	-0.840229649
ATP6V0E	NM_003945	-0.767172561
AXL	NM_001699 /// NM_021913	0.716372713
B4GALT1	NM_001497	0.748412221
B4GALT6	NM_004775	-0.751906998
BCL10	NM_003921	-1.045655594
BNIP3L	NM_004331	-1.532819556
BRCA1	NM_007294 /// NM_007295 /// NM_007296 /// NM_007297 /// NM_007298 /// NM_007299	-1.140217631
C6orf120	NM_001029863	0.876394834
C6orf155	NM_024882	2.201467936
C6orf210	NM_020381	-1.311623155
CAV2	NM_001233 /// NM_198212	-1.248062997
CCDC28A	NM_015439	-1.961620584
CCL2	NM_002982	0.948633123
CCNG1	NM_004060 /// NM_199246	0.727459368
CD38	NM_001775	1.149396658
CDK4	NM_000075	-0.963112257
CDK8	NM_001260	-0.707005685
CFH /// CFHL1	NM_000186 /// NM_001014975 /// NM_002113	0.705005921
CHMP5	NM_016410	-1.113320389
COL11A1	NM_001854 /// NM_080629 /// NM_080630	1.06415718
CPM	NM_001005502 /// NM_001874 /// NM_198320	-0.727000106
CPS1	NM_001875	0.890327068
CREB3L2	NM_194071	-1.147859524
CTH	NM_001902 /// NM_153742	-0.724838822
CXCL3	NM_002090	0.905175084
CXCL5	NM_002994	1.237295089
DIO2	NM_000793 /// NM_001007023 /// NM_013989	-0.731070381
DKFZp434H1419	---	-1.213095446
EGFR	NM_005228 /// NM_201282 /// NM_201283 /// NM_201284	0.873087099
EI24	NM_001007277 /// NM_004879	-1.056093529
EIF2S1	NM_004094	-0.894987495
F5	NM_000130	0.983748404
FAM45B /// FAM45A	NM_018472 /// NM_207009	-1.216895124
FAS	NM_000043 /// NM_152871 /// NM_152872 /// NM_152873 /// NM_152874 /// NM_152875	0.720304251
FCHO1	NM_015122	-1.035564154
FEZ2	NM_005102	-1.540032542
FLJ13912	NM_022770	-1.058436981

GALNT1	NM_020474	-1.03022635
GLIPR1	NM_006851	0.771047501
GMDS	NM_001500	-0.706432221
GPR107	NM_020960	1.329247979
GPR64	NM_005756	1.226872143
GREM1	NM_013372	-2.141146329
HDAC3	NM_003883	-1.188428452
HIC2	NM_015094	0.848647375
HIST1H2BC	NM_003526	1.138396492
IDI1	NM_004508	-0.952048161
IL6ST	NM_002184 /// NM_175767	0.825888288
IQGAP2	NM_006633	0.922666241
ITGB6	NM_000888	0.972580772
JUN	NM_002228	-0.989407999
KCNJ16	NM_018658 /// NM_170741 /// NM_170742	0.70784406
LOC440118	XM_498554	1.029719744
MAP7	NM_003980	0.710328186
METAP2	NM_006838	-0.781506981
MGC4172	NM_024308	-0.801783402
MPHOSPH6	NM_005792	-1.053817598
NCF2	NM_000433	-0.762923633
NF1	NM_000267	-1.659565398
NFYC	NM_014223	-0.96189603
NR2F1	NM_005654	0.769244922
NTS	NM_006183	1.139774547
NUDT15	NM_018283	-1.037811863
PAPPA	NM_002581	0.762370796
PCTK1	NM_006201 /// NM_033018	-1.324652844
PDCD2	NM_002598 /// NM_144781	-1.515603224
PHF10	NM_018288 /// NM_133325	-1.030400448
PIR	NM_001018109 /// NM_003662	-2.705431095
PLA2G4A	NM_024420	0.8022221
PLEKHA1	NM_001001974 /// NM_021622	-0.700145946
PPP1CB	NM_002709 /// NM_206876 /// NM_206877	-0.864483881
PSF1	NM_021067	-1.366589197
PTGS2	NM_000963	0.764713826
RARRES1	NM_002888 /// NM_206963	0.703593775
RGC32	NM_014059	0.744611688
RP2	NM_006915	-0.882482368
RPS6KA5	NM_004755 /// NM_182398	-0.712952845
RRAGC	NM_022157	0.713512091
RRM2	NM_001034	-0.876164389
SCD	NM_005063	0.888437407
SDC4	NM_002999	-1.014133325
SEMA3C	NM_006379	0.768322613
SESN1	NM_014454	0.717889134
SGPP1	NM_030791	-1.162308463
SLC1A1	NM_004170	-0.788724519
SLC2A3	NM_006931	-0.708665576
SNAP25	NM_003081 /// NM_130811	1.297734799
SNRPD1	NM_006938	-1.550409311
SOX18	NM_018419	1.809239926

SPRY4	NM_030964	1.038107336
SSB	NM_003142	-1.245450605
ST7	NM_018412 /// NM_021908	-1.117947704
SWAP70	NM_015055	-0.918387597
SYT1	NM_005639	0.719749608
TEAD1	NM_021961	1.268097038
TGFBR3	NM_003243	0.773893351
TIPRL	NM_001031800 /// NM_152902	-1.922938983
TMC5	NM_024780	-0.874298517
TNC	NM_002160	0.923411097
TOP1	NM_003286	0.738270072
TTC10	NM_006531 /// NM_175605	-0.799418273
TTMP	NM_024616	0.867103058
TTRAP	NM_016614	-1.148845268
UBE2V2	NM_003350	-0.750839256
UBN1	NM_016936	-1.060787199
VAV3	NM_006113	0.753855057
WIG1	NM_022470 /// NM_152240	0.737324985
WISP2	NM_003881	-0.724955794

Table 1I. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR hsa-miR-331.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**$\Delta \log_2$**
ADAM9	NM_001005845 /// NM_003816	-1.018202582
AMBP	NM_001633	0.713506969
ANKRD46	NM_198401	0.758769458
AQP3	NM_004925	-1.251852727
AR	NM_000044 /// NM_001011645	-0.778339604
AREG	NM_001657	-0.753449628
ARHGDIA	NM_004309	-0.951679694
ARL2BP	NM_012106	0.996494605
ATP6V0E	NM_003945	1.367616054
AVPI1	NM_021732	-0.751596798
B4GALT4	NM_003778 /// NM_212543	-0.753713587
BAMBI	NM_012342	-1.255265115
BCL2L1	NM_001191 /// NM_138578	-0.886454677
BICD2	NM_001003800 /// NM_015250	-1.182358353
C19orf10	NM_019107	-1.53899451
C1orf24	NM_022083 /// NM_052966	-0.704802929
C2orf25	NM_015702	-1.081072862
CASP7	NM_001227 /// NM_033338 /// NM_033339 /// NM_033340	-1.026901276
CCNG1	NM_004060 /// NM_199246	0.897682498
CDS1	NM_001263	-0.795343714
CDS2	NM_003818	-0.781611289
CFH	NM_000186 /// NM_001014975	-0.703427241
CGI-48	NM_016001	1.289624084
CLN5	NM_006493	-1.466578653
COL4A2	NM_001846	-0.805438025
COMMD9	NM_014186	-1.028582082
COQ2	NM_015697	-1.037753576

CSF2RA	NM_006140 /// NM_172245 /// NM_172246 /// NM_172247 /// NM_172248 /// NM_172249	-0.820735805
CXCL1	NM_001511	0.989718005
D15Wsu75e	NM_015704	-1.230678591
DAF	NM_000574	-1.116320814
DDAH1	NM_012137	0.702333256
DIO2	NM_000793 /// NM_001007023 /// NM_013989	-0.818111915
DSU	NM_018000	0.921680342
EEF1D	NM_001960 /// NM_032378	0.754057576
EFNA1	NM_004428 /// NM_182685	0.811485975
EHD1	NM_006795	-1.128885271
EIF5A2	NM_020390	-1.220164668
EMP1	NM_001423	-1.148241753
ENO1	NM_001428	0.78630193
EREG	NM_001432	-0.762145502
FAM63B	NM_019092	-1.181178296
FBXO11	NM_012167 /// NM_018693 /// NM_025133	0.812682335
FGFR1	NM_000604 /// NM_015850 /// NM_023105 /// NM_023106 /// NM_023107 /// NM_023108	-1.002378067
FOSL1	NM_005438	-0.913695565
GALNT7	NM_017423	-0.745195648
GATA6	NM_005257	-1.045711005
GGT1	NM_001032364 /// NM_001032365 /// NM_005265 /// NM_013430	-1.113140527
GLRB	NM_000824	-1.060497998
GPR64	NM_005756	-0.758625112
GUK1	NM_000858	-1.13218881
HAS2	NM_005328	-0.762816377
HKDC1	NM_025130	-0.949792861
HLRC1	NM_031304	-1.097296685
HMGA1	NM_002131 /// NM_145899 /// NM_145901 /// NM_145902 /// NM_145903 /// NM_145904	-0.880292199
HSPA4	NM_002154 /// NM_198431	0.728696496
HSPB8	NM_014365	-0.759977773
HSPC009	---	-1.03607819
IGFBP3	NM_000598 /// NM_001013398	-0.845378586
IL13RA1	NM_001560	-2.196282315
IL32	NM_001012631 /// NM_001012632 /// NM_001012633 /// NM_001012634 /// NM_001012635	0.833485752
IL6R	NM_000565 /// NM_181359	-0.914757761
IL8	NM_000584	0.913397477
INHBC	NM_005538	0.858995384
ITGB4	NM_000213 /// NM_001005619 /// NM_001005731	-0.85799549
KIAA0090	NM_015047	-1.164407472
KIAA1164	NM_019092	-1.23704637
KIAA1641	NM_020970	-0.836514008
KLF4	NM_004235	-1.055039556
LMO4	NM_006769	-1.107321559
LOC137886	XM_059929	-1.123182493
LOXL2	NM_002318	-1.209767441
LRP3	NM_002333	-0.715117868
MARCKS	NM_002356	-1.469677149

MAZ	NM_002383	-1.126821745
MCL1	NM_021960 /// NM_182763	0.942257941
MGAM	NM_004668	-0.814502675
MGC3196	XM_495878	-1.126417939
MGC3260	---	-1.025699392
MGC4172	NM_024308	-0.913455714
MICAL2	NM_014632	-1.082050523
MTMR1	NM_003828 /// NM_176789	-0.735120951
NEFL	NM_006158	-0.717701382
NPTX1	NM_002522	0.75531673
NR5A2	NM_003822 /// NM_205860	-0.986400711
NUCKS	NM_022731	1.878690008
NUDT15	NM_018283	-0.73413178
OXTR	NM_000916	-0.706995427
P4HB	NM_000918	-1.115420821
PDCD4	NM_014456 /// NM_145341	-0.703141449
PDPK1	NM_002613 /// NM_031268	-0.997800492
PDZK1IP1	NM_005764	0.899109852
PGK1	NM_000291	1.458474231
PHLPP	NM_194449	-1.08805252
PIG8	NM_014679	-1.143792856
PLD3	NM_001031696 /// NM_012268	-1.061520584
PLEC1	NM_000445 /// NM_201378 /// NM_201379 /// NM_201380 /// NM_201381 /// NM_201382	-0.861657517
PLEKHA1	NM_001001974 /// NM_021622	-0.814352719
PMCH	NM_002674	1.23471474
PODXL	NM_001018111 /// NM_005397	-0.759679646
PPL	NM_002705	-0.863943433
PRCC	NM_005973 /// NM_199416	-1.560043378
PRO1843	---	1.024656281
PTENP1	---	0.843987346
PTPN12	NM_002835	0.720770416
PXN	NM_002859	-0.906771926
RAB2	NM_002865	1.21822883
RGS2	NM_002923	-0.751864654
RHEB	NM_005614	1.032801782
RHOBTB1	NM_001032380 /// NM_014836 /// NM_198225	-1.461092343
RIP	NM_001033002 /// NM_032308	1.32081268
RPA2	NM_002946	-1.930005451
RPE	NM_006916 /// NM_199229	-1.035661937
RPE /// LOC440001	NM_006916 /// NM_199229 /// XM_495848	-1.348584718
RPL14	NM_001034996 /// NM_003973	0.889103758
RPL38	NM_000999	1.195046989
RPS11	NM_001015	0.966761487
RRBP1	NM_004587	-1.58296738
SAV1	NM_021818	-1.200930354
SDC4	NM_002999	-0.943854956
SDHB	NM_003000	-0.795591847
SEPT9	NM_006640	-1.476797247
SH3YL1	NM_015677	0.797572491
SLC7A1	NM_003045	-1.030604814

SMA4	NM_021652	-0.777526871
SS18	NM_001007559 /// NM_005637	-1.164712195
STX6	NM_005819	-0.793475858
SUMO2	NM_001005849 /// NM_006937	0.809404068
SYNJ2BP	NM_018373	-1.058973759
TBC1D16	NM_019020	-0.823007164
TBC1D2	NM_018421	-0.805664472
TFG	NM_001007565 /// NM_006070	0.963221751
TFPI	NM_001032281 /// NM_006287	-0.848767621
TGFB2	NM_003238	-1.04497232
THBS1	NM_003246	-1.083274383
TMC5	NM_024780	-1.012924338
TMEM2	NM_013390	-1.011217086
TMEM45A	NM_018004	-0.789448041
TMF1	NM_007114	-1.180142228
TNC	NM_002160	-0.703964402
TNFAIP6	NM_007115	-1.1186537
TNFSF9	NM_003811	-0.982271707
TOR1AIP1	NM_015602	-0.919343306
TOX	NM_014729	-0.723074509
TRA1	NM_003299	1.696864298
TRFP	NM_004275	-1.030283612
TRIP13	NM_004237	-0.809487394
TRPC1	NM_003304	-0.751661455
TTC3	NM_001001894 /// NM_003316	-0.703114676
TXLNA	NM_175852	-1.477978781
TXN	NM_003329	1.338245007
UGT1A8 /// UGT1A9	NM_019076 /// NM_021027	-0.881758515
USP46	NM_022832	-1.106506898
VANGL1	NM_138959	-0.946441805
VDAC3	NM_005662	0.840449353
VIL2	NM_003379	0.706193269
WDR1	NM_005112 /// NM_017491	-0.739441224
WNT7B	NM_058238	-0.891232207
WSB2	NM_018639	0.720487526
XTP2	NM_015172	0.708257434
YRDC	NM_024640	-1.09546979
ZMYM6	NM_007167	-1.435718926
ZNF259	NM_003904	-1.233812004
ZNF395	NM_018660	-1.233741599

Table 1J. Genes with increased (positive values) or decreased (negative values) expression following transfection of human cancer cells with pre-miR mmu-miR-292-3p.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**$\Delta \log_2$**
ABCA12	NM_015657 /// NM_173076	1.274537758
ACAA1	NM_001607	-1.341988411
ADRB2	NM_000024	0.734681598
AHNAK	NM_001620 /// NM_024060	-1.068047951
AKR7A2	NM_003689	-1.260890028
ALDH3A2	NM_000382 /// NM_001031806	-1.149835407

ALDH6A1	NM_005589	0.707556281
AP1G1	NM_001030007 /// NM_001128	-1.091995963
AP1S2	NM_003916	-1.261719242
AR	NM_000044 /// NM_001011645	-1.016538203
ARCN1	NM_001655	-1.394989314
ARHGDIA	NM_004309	-1.088113999
ARL2BP	NM_012106	0.850663075
ASNS	NM_001673 /// NM_133436 /// NM_183356	-1.143388594
ATF5	NM_012068	-1.313158757
ATP6V0E	NM_003945	1.7283045
B3GNT3	NM_014256	-0.749527176
B4GALT6	NM_004775	-0.977953158
BCL2A1	NM_004049	1.206247671
BDKRB2	NM_000623	1.061713745
BICD2	NM_001003800 /// NM_015250	-1.258118547
BIRC3	NM_001165 /// NM_182962	1.060985056
BPGM	NM_001724 /// NM_199186	-1.860577967
BRP44	NM_015415	-1.286540106
BTG2	NM_006763	1.379663209
C14orf2	NM_004894	-1.247503837
C19orf2	NM_003796 /// NM_134447	-1.41536794
C1GALT1C1	NM_001011551 /// NM_152692	-1.194583625
C1orf121	NM_016076	-0.734943568
C1R	NM_001733	1.15987472
C20orf27	NM_017874	-0.745064444
C21orf25	NM_199050	0.743360022
C2orf17	NM_024293	-1.510848665
C2orf26	NM_023016	-1.019347994
C3	NM_000064	2.06034744
C6orf210	NM_020381	-1.32460427
C8orf1	NM_004337	0.722461307
CA11	NM_001217	-0.871451676
CALM1	NM_006888	-1.352507852
CASP7	NM_001227 /// NM_033338 /// NM_033339 /// NM_033340	-0.810273138
CCL20	NM_004591	1.15656517
CCND3	NM_001760	-0.782111615
CCNG1	NM_004060 /// NM_199246	1.387659998
CD44	NM_000610 /// NM_001001389 /// NM_001001390 /// NM_001001391 /// NM_001001392	0.719455355
CDH4	NM_001794	-1.430091267
CEBPD	NM_005195	1.006214661
CFH /// CFHL1	NM_000186 /// NM_001014975 /// NM_002113	-1.50657812
CGI-48	NM_016001	1.518000296
CLIC4	NM_013943	1.141308993
CLU	NM_001831 /// NM_203339	-0.808510733
COL5A1	NM_000093	0.838721257
COPS6	NM_006833	-2.469125346
COQ2	NM_015697	-1.820118826
CPM	NM_001005502 /// NM_001874 /// NM_198320	1.811763795
CSF1	NM_000757 /// NM_172210 /// NM_172211 /// NM_172212	1.093739444

CTDSP2	NM_005730	1.1038569
CXCL1	NM_001511	1.373132066
CXCL2	NM_002089	1.348536544
CXCL3	NM_002090	1.015075683
CXCL5	NM_002994	0.943452807
CYP4F3	NM_000896	-0.944098228
CYP51A1	NM_000786	1.017134253
DAAM1	NM_014992	1.296531572
DAZAP2	NM_014764	-1.658661628
DAZAP2 /// LOC401029	NM_014764 /// XM_376165	-1.087782444
DCP2	NM_152624	1.77586343
DIPA	NM_006848	-0.93403737
DKFZP564J0123	NM_199069 /// NM_199070 /// NM_199073 /// NM_199074 /// NM_199417	-1.383450396
DKK3	NM_001018057 /// NM_013253 /// NM_015881	0.878239299
DMN	NM_015286 /// NM_145728	-1.141858838
DNAJB4	NM_007034	-1.296695319
DPYSL4	NM_006426	1.395487959
DST	NM_001723 /// NM_015548 /// NM_020388 /// NM_183380	0.826671369
DSU	NM_018000	0.850899944
DTYMK	NM_012145	-1.318162355
DUSP3	NM_004090	-1.089273702
E2F8	NM_024680	-1.013925338
EEF1D	NM_001960 /// NM_032378	0.921658799
EFEMP1	NM_004105 /// NM_018894	0.72566566
EFNA1	NM_004428 /// NM_182685	2.046925472
EGFL4	NM_001410	-1.078181988
EHF	NM_012153	-0.797518709
EIF2C1	NM_012199	-1.057953517
ELOVL6	NM_024090	0.700401502
ENO1	NM_001428	0.815326156
ENTPD7	NM_020354	1.034032191
FAM46A	NM_017633	0.898362379
FAM63B	NM_019092	0.727540952
FAS	NM_000043 /// NM_152871 /// NM_152872 /// NM_152873 /// NM_152874 /// NM_152875	1.579115853
FBLN1	NM_001996 /// NM_006485 /// NM_006486 /// NM_006487	-1.342132018
FBXO11	NM_012167 /// NM_018693 /// NM_025133	0.981097713
FDXR	NM_004110 /// NM_024417	1.164440342
FEZ2	NM_005102	-0.975086128
FGFBP1	NM_005130	0.74848828
FLJ11259	NM_018370	0.775722888
FLJ13236	NM_024902	-1.279533014
FLJ13910	NM_022780	0.737477028
FLJ22662	NM_024829	-1.298342375
FNBP1	NM_015033	0.792859874
FOSL1	NM_005438	0.70494518
GALE	NM_000403 /// NM_001008216	-1.680052376
GAS2L1	NM_006478 /// NM_152236 /// NM_152237	-1.089734346
GCLC	NM_001498	-1.212645403

GFPT2	NM_005110	0.739403227
GLT25D1	NM_024656	-1.128968664
GLUL	NM_001033044 /// NM_001033056 /// NM_002065	0.707890594
GMDS	NM_001500	-1.062449288
GMPR2	NM_001002000 /// NM_001002001 /// NM_001002002 /// NM_016576	-1.139237339
GNA13	NM_006572	1.236589519
GOLPH2	NM_016548 /// NM_177937	-1.086755929
GPI	NM_000175	-1.259439873
GPNMB	NM_001005340 /// NM_002510	-1.007595602
GREB1	NM_014668 /// NM_033090 /// NM_148903	1.352108534
GSPT1	NM_002094	-1.044364422
HAS2	NM_005328	0.947721212
HBXIP	NM_006402	-1.031037958
HIC2	NM_015094	1.023623547
HIST1H2AC	NM_003512	-1.008238017
HLA-DMB	NM_002118	-0.775827225
HMGA2	NM_001015886 /// NM_003483 /// NM_003484	1.304771857
HMGCR	NM_000859	1.27304615
HMGCS1	NM_002130	1.012886882
HMMR	NM_012484 /// NM_012485	-0.70033762
HMOX1	NM_002133	-1.35301396
HNMT	NM_001024074 /// NM_001024075 /// NM_006895	1.041235328
HSPCA	NM_001017963 /// NM_005348	-1.074857802
ID1	NM_002165 /// NM_181353	-1.025496584
ID2	NM_002166	-0.705177884
IDI1	NM_004508	1.219263646
IDS	NM_000202 /// NM_006123	-1.077198338
IER3IP1	NM_016097	0.940286614
IGFBP3	NM_000598 /// NM_001013398	-1.610733561
IL1RAP	NM_002182 /// NM_134470	1.347581197
IL32	NM_001012631 /// NM_001012632 /// NM_001012633 /// NM_001012634 /// NM_001012635	2.250504431
IL6R	NM_000565 /// NM_181359	1.202516814
IL8	NM_000584	1.738888969
INHBB	NM_002193	-0.789026545
INHBC	NM_005538	1.054375714
INSIG1	NM_005542 /// NM_198336 /// NM_198337	1.312569861
INSL4	NM_002195	-0.968255432
IPO7	NM_006391	-1.137292191
ITGB4	NM_000213 /// NM_001005619 /// NM_001005731	-1.241875014
KCNJ16	NM_018658 /// NM_170741 /// NM_170742	-0.994177169
KIAA0317	NM_014821	-1.954785599
KIAA0485	---	0.803437158
KIAA0882	NM_015130	0.886522516
KIAA1164	NM_019092	1.106110788
KLC2	NM_022822	-0.929423697
KRT7	NM_005556	0.876412052
LAMP1	NM_005561	-1.347563751

LEPR	NM_001003679 /// NM_001003680 /// NM_002303	-0.883786823
LMO4	NM_006769	-0.899001385
LOC440118	XM_498554	2.659402205
LRP8	NM_001018054 /// NM_004631 /// NM_017522 /// NM_033300	-0.913541429
MAFF	NM_012323 /// NM_152878	1.037660909
MAP3K6	NM_004672	-1.020561565
MAPKAPK2	NM_004759 /// NM_032960	-0.851240177
MARCH2	NM_001005415 /// NM_001005416 /// NM_016496	-1.340797948
MAT2B	NM_013283 /// NM_182796	-1.010823059
MCAM	NM_006500	0.761721492
MCL1	NM_021960 /// NM_182763	1.676669192
MDM2	NM_002392 /// NM_006878 /// NM_006879 /// NM_006880 /// NM_006881 /// NM_006882	1.177412993
MERTK	NM_006343	0.794000917
MGC2574	NM_024098	-1.346847468
MGC5508	NM_024092	-1.272547011
MGC5618	---	1.428865355
MICAL-L1	NM_033386	1.230207682
MPV17	NM_002437	-1.076584476
MR1	NM_001531	1.030488179
MTDH	NM_178812	-1.117806598
MVP	NM_005115 /// NM_017458	-0.709666753
NALP1	NM_001033053 /// NM_014922 /// NM_033004 /// NM_033006 /// NM_033007	0.805360321
NEFL	NM_006158	0.936792696
NID1	NM_002508	1.050433438
NMU	NM_006681	-0.895973974
NPR3	NM_000908	0.847545931
NR2F2	NM_021005	-1.05195379
NR4A2	NM_006186 /// NM_173171 /// NM_173172 /// NM_173173	-0.784394334
NUCKS	NM_022731	2.054851809
NUMA1	NM_006185	-0.935775914
NUPL1	NM_001008564 /// NM_001008565 /// NM_014089	0.995356442
OPTN	NM_001008211 /// NM_001008212 /// NM_001008213 /// NM_021980	1.062219148
ORMDL2	NM_014182	-1.234447987
P4HA2	NM_001017973 /// NM_001017974 /// NM_004199	0.911666974
PAFAH1B2	NM_002572	-1.046822403
PAPPA	NM_002581	0.729791369
PAQR3	NM_177453	-1.033326915
PDCD2	NM_002598 /// NM_144781	-0.961233896
PDCD4	NM_014456 /// NM_145341	0.7201252
PDCD6IP	NM_013374	-1.196552647
PDGFRL	NM_006207	0.893046656
PEX10	NM_002617 /// NM_153818	-1.116287896
PGK1	NM_000291	1.670142045
PHTF2	NM_020432	0.925243951
PIGK	NM_005482	-1.409798998

PLAT	NM_000930 /// NM_000931 /// NM_033011	0.929497265
PLAU	NM_002658	1.066687801
PLEKHA1	NM_001001974 /// NM_021622	0.910943491
PLSCR4	NM_020353	0.724455918
PMCH	NM_002674	1.270137987
PODXL	NM_001018111 /// NM_005397	1.036062602
POLR3D	NM_001722	-1.115693639
POLR3G	NM_006467	-0.761975143
PON2	NM_000305 /// NM_001018161	-1.276679882
PON3	NM_000940	-0.74811781
PPAP2C	NM_003712 /// NM_177526 /// NM_177543	-1.291995651
PPM1D	NM_003620	1.299946946
PRDX6	NM_004905	-1.304368229
PREI3	NM_015387 /// NM_199482	-1.905696629
PRNP	NM_000311 /// NM_183079	-1.121128917
PRO1843	---	1.272144805
PSIP1	NM_021144 /// NM_033222	-1.013912911
PTEN	NM_000314	-1.24087728
PTER	NM_001001484 /// NM_030664	-1.11747507
PTK9	NM_002822 /// NM_198974	1.126567447
PTMS	NM_002824	-0.888918542
PTP4A1	NM_003463	1.05405477
PTPN12	NM_002835	0.974469072
PTX3	NM_002852	1.329740901
PXDN	XM_056455	1.024115421
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.851419246
RAB13	NM_002870	-1.03691008
RAB2	NM_002865	1.28227173
RAB32	NM_006834	-1.021658289
RAB4A	NM_004578	-1.275775048
RAP140	NM_015224	-1.085805474
RASGRP1	NM_005739	1.023197964
RBP4	NM_006744	1.066069203
RDX	NM_002906	1.366314325
RHEB	NM_005614	1.061183478
RIG	---	1.098716654
RIP	NM_001033002 /// NM_032308	1.131269937
RNF141	NM_016422	-1.263130303
RPL14	NM_001034996 /// NM_003973	0.872264327
RPL38	NM_000999	1.275185495
RPS11	NM_001015	0.988294482
RRAD	NM_004165	0.714605352
RRAGC	NM_022157	1.010062922
RRAGD	NM_021244	1.271449795
RRM2	NM_001034	-1.903220473
SAMD4	NM_015589	1.225116813
SC4MOL	NM_001017369 /// NM_006745	1.373112547
SCARB2	NM_005506	1.116638678
SCD	NM_005063	1.110346934
SCML1	NM_006746	1.225870611
SDHA	NM_004168	-1.052892397

SEC23A	NM_006364	-0.818184343
SESN1	NM_014454	1.543653494
SH3GLB2	NM_020145	-0.903986408
SKP2	NM_005983 /// NM_032637	1.381913073
SLC11A2	NM_000617	0.946254297
SLC2A3	NM_006931	1.313395241
SLC2A3 /// SLC2A14	NM_006931 /// NM_153449	1.052490023
SLC30A9	NM_006345	-1.322099941
SLC35A3	NM_012243	-1.013644493
SMARCA2	NM_003070 /// NM_139045	0.801377135
SNRPD1	NM_006938	-0.865130985
SOD2	NM_000636 /// NM_001024465 /// NM_001024466	1.214392447
SORBS3	NM_001018003 /// NM_005775	-1.090614527
SOX18	NM_018419	4.148048165
SPARC	NM_003118	1.52156486
SPHAR	NM_006542	-0.926094726
SQLE	NM_003129	1.043028372
SRPX	NM_006307	0.79067552
STC1	NM_003155	1.02010396
STK24	NM_001032296 /// NM_003576	-0.828653609
STS	NM_000351	-1.150824058
STX3A	NM_004177	0.959801577
SUCLG2	NM_003848	-1.642142769
SUMO2	NM_001005849 /// NM_006937	0.867682532
SVIL	NM_003174 /// NM_021738	0.760443698
SYT1	NM_005639	-1.220961769
TAF15	NM_003487 /// NM_139215	0.839954321
TBC1D2	NM_018421	-0.925351913
TDG	NM_001008411 /// NM_003211	0.810140453
TFG	NM_001007565 /// NM_006070	1.057373538
TFPI	NM_001032281 /// NM_006287	0.999943519
TFRC	NM_003234	-1.062533788
TGFBR3	NM_003243	1.021115746
THBS1	NM_003246	-1.182821435
TJP2	NM_004817 /// NM_201629	0.832785426
TK2	NM_004614	-1.219573893
TM4SF20	NM_024795	-1.052929883
TM4SF4	NM_004617	-1.214905307
TM7SF1	NM_003272	-0.921538795
TncRNA	---	1.510437605
TNFAIP3	NM_006290	1.049000444
TNFAIP6	NM_007115	-1.137303144
TNFRSF10B	NM_003842 /// NM_147187	1.00601181
TNFRSF9	NM_001561	0.879508972
TNS1	NM_022648	1.429582253
TPD52L1	NM_001003395 /// NM_001003396 /// NM_001003397 /// NM_003287	-1.052818746
TPI1	NM_000365	-1.042595069
TPM4	NM_003290	-1.1018669
TRA1	NM_003299	2.06266927

TRIM14	NM_014788 /// NM_033219 /// NM_033220 /// NM_033221	-1.348327164
TTMP	NM_024616	-0.79505753
TXLNA	NM_175852	-0.989673731
TXN	NM_003329	1.418205452
UBE2V2	NM_003350	-1.116103021
USP46	NM_022832	-1.625223999
VDAC1	NM_003374	-1.70629034
VDAC3	NM_005662	0.95727826
VIL2	NM_003379	-1.38536373
VPS4A	NM_013245	-0.759414556
WBSCR22	NM_017528	-1.011859709
WDR7	NM_015285 /// NM_052834	-1.206634395
WEE1	NM_003390	1.163396761
WIG1	NM_022470 /// NM_152240	0.700863484
WIZ	XM_372716	-1.129981905
WNT7B	NM_058238	-1.794403919
WSB2	NM_018639	1.487026325
XTP2	NM_015172	0.895652638
YIPF3	NM_015388	-1.060355879
YOD1	NM_018566	1.018605664
ZNF259	NM_003904	-0.79681991
ZNF652	NM_014897	0.854709863

A further embodiment of the invention is directed to methods of modulating a cellular pathway comprising administering to the cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence or a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor. A cell, tissue, or subject may be a cancer cell, a cancerous tissue or harbor cancerous tissue, or a cancer patient. The database content related to all nucleic acids and genes designated by an accession number or a database submission are incorporated herein by reference as of the filing date of this application.

A further embodiment of the invention is directed to methods of modulating a cellular pathway comprising administering to the cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence in an amount sufficient to modulate the expression, function, status, or state of a cellular pathway, in particular those pathways described in Table 2 or the pathways known to include one or more genes from Table 1, 3, and/or 4. Modulation of a cellular pathway includes, but is not limited to modulating the expression of one or more gene(s). Modulation of a gene can include inhibiting the function of an endogenous miRNA or

providing a functional miRNA to a cell, tissue, or subject. Modulation refers to the expression levels or activities of a gene or its related gene product (*e.g.*, mRNA) or protein, *e.g.*, the mRNA levels may be modulated or the translation of an mRNA may be modulated. Modulation may increase or up regulate a gene or gene product or it may decrease or down regulate a gene or gene product (*e.g.*, protein levels or activity).

Still a further embodiment includes methods of administering an miRNA or mimic thereof, and/or treating a subject or patient having, suspected of having, or at risk of developing a pathological condition comprising one or more of step (a) administering to a patient or subject an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p nucleic acid sequence or a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor in an amount sufficient to modulate expression of a cellular pathway; and (b) administering a second therapy, wherein the modulation of the cellular pathway sensitizes the patient or subject, or increases the efficacy of a second therapy. An increase in efficacy can include a reduction in toxicity, a reduced dosage or duration of the second therapy, or an additive or synergistic effect. A cellular pathway may include, but is not limited to one or more pathway described in Table 2 below or a pathway that is know to include one or more genes of Tables 1, 3, and/or 4. The second therapy may be administered before, during, and/or after the isolated nucleic acid or miRNA or inhibitor is administered.

A second therapy can include administration of a second miRNA or therapeutic nucleic acid such as a siRNA or antisense oligonucleotide, or may include various standard therapies, such as pharmaceuticals, chemotherapy, radiation therapy, drug therapy, immunotherapy, and the like. Embodiments of the invention may also include the determination or assessment of gene expression or gene expression profile for the selection of an appropriate therapy. In a particular aspect, a second therapy is chemotherapy. A chemotherapy can include, but is not limited to paclitaxel, cisplatin, carboplatin, doxorubicin, oxaliplatin, larotaxel, taxol, lapatinib, docetaxel, methotrexate, capecitabine, vinorelbine, cyclophosphamide, gemcitabine, amrubicin, cytarabine, etoposide, camptothecin, dexamethasone, dasatinib, tipifarnib,

bevacizumab, sirolimus, temsirolimus, everolimus, lonafarnib, cetuximab, erlotinib, gefitinib, imatinib mesylate, rituximab, trastuzumab, nocodazole, sorafenib, sunitinib, bortezomib, alemtuzumab, gemtuzumab, tositumomab or ibritumomab.

Embodiments of the invention include methods of treating a subject with a disease or condition comprising one or more of the steps of (a) determining an expression profile of one or more genes selected from Table 1, 3, and/or 4; (b) assessing the sensitivity of the subject to therapy based on the expression profile; (c) selecting a therapy based on the assessed sensitivity; and (d) treating the subject using a selected therapy. Typically, the disease or condition will have as a component, indicator, or resulting mis-regulation of one or more gene of Table 1, 3, and/or 4.

In certain aspects, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more miRNA may be used in sequence or in combination; for instance, any combination of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor with another miRNA or miRNA inhibitor. Further embodiments include the identification and assessment of an expression profile indicative of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p status in a cell or tissue comprising expression assessment of one or more gene from Table 1, 3, and/or 4, or any combination thereof.

The term "miRNA" is used according to its ordinary and plain meaning and refers to a microRNA molecule found in eukaryotes that is involved in RNA-based gene regulation. See, *e.g.*, Carrington *et al.*, 2003, which is hereby incorporated by reference. The term can be used to refer to the single-stranded RNA molecule processed from a precursor or in certain instances the precursor itself.

In some embodiments, it may be useful to know whether a cell expresses a particular miRNA endogenously or whether such expression is affected under particular conditions or when it is in a particular disease state. Thus, in some embodiments of the invention, methods include assaying a cell or a sample containing a cell for the presence of one or more marker gene or mRNA or other analyte indicative of the expression level of a gene of interest. Consequently, in some

embodiments, methods include a step of generating an RNA profile for a sample. The term "RNA profile" or "gene expression profile" refers to a set of data regarding the expression pattern for one or more gene or genetic marker or miRNA in the sample (*e.g.*, a plurality of nucleic acid probes that identify one or more markers from Tables 1, 3, and/or 4); it is contemplated that the nucleic acid profile can be obtained using a set of RNAs, using for example nucleic acid amplification or hybridization techniques well know to one of ordinary skill in the art. The difference in the expression profile in the sample from the patient and a reference expression profile, such as an expression profile of one or more genes or miRNAs, are indicative of which miRNAs to be administered.

In certain aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and let-7 or let-7 inhibitor can be administered to patients with with acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, bladder carcinoma, cervical carcinoma, carcinoma of the head and neck, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, Kaposi's sarcoma, leukemia, lung carcinoma, leiomyosarcoma, melanoma, medulloblastoma, myxofibrosarcoma, multiple myeloma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, pancreatic carcinoma, prostate carcinoma, squamous cell carcinoma of the head and neck, salivary gland tumor, thyroid carcinoma, and/or urothelial carcinoma.

Further aspects include administering miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-15 or miR-15 inhibitor to patients with astrocytoma, acute myeloid leukemia, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, carcinoma of the head and neck, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, hepatoblastoma, hepatocellular carcinoma, Hodgkin lymphoma, lung carcinoma,

laryngeal squamous cell carcinoma, larynx carcinoma, melanoma, mantle cell lymphoma, myxofibrosarcoma, myeloid leukemia, multiple myeloma, neuroblastoma, neurofibroma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, and/or thyroid carcinoma.

In still further aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-16 or miR-16 inhibitor are administered to patients with astrocytoma, breast carcinoma, B-cell lymphoma, bladder carcinoma, colorectal carcinoma, endometrial carcinoma, glioblastoma, gastric carcinoma, hepatoblastoma, hepatocellular carcinoma, Hodgkin lymphoma, laryngeal squamous cell carcinoma, melanoma, medulloblastoma, mantle cell lymphoma, myxofibrosarcoma, myeloid leukemia, multiple myeloma, neurofibroma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, and/or thyroid carcinoma.

In certain aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-20 or miR-20 inhibitor are administered to patients with astrocytoma, acute myeloid leukemia, breast carcinoma, bladder carcinoma, cervical carcinoma, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, leukemia, lipoma, melanoma, mantle cell lymphoma, myxofibrosarcoma, multiple myeloma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, squamous cell carcinoma of the head and neck, thyroid carcinoma, and/or urothelial carcinoma.

Aspects of the invention include methods where miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or

miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-21 or miR-21 inhibitor are administered to patients with astrocytoma, acute lymphoblastic leukemia, acute myeloid leukemia, breast carcinoma, Burkitt's lymphoma, bladder carcinoma, colorectal carcinoma, endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, melanoma, mantle cell lymphoma, myeloid leukemia, neuroblastoma, neurofibroma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, and/or squamous cell carcinoma of the head and neck.

In still further aspects, miR-15, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-26a or miR-26a inhibitor are administered to patients with anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, B-cell lymphoma, Burkitt's lymphoma, bladder carcinoma, cervical carcinoma, carcinoma of the head and neck, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Kaposi's sarcoma, leukemia, lung carcinoma, leiomyosarcoma, larynx carcinoma, melanoma, multiple myeloma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, and/or testicular tumor.

In yet a further aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-34a or miR-34a inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, carcinoma of the head and neck, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma,

endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, gastrinoma, hepatoblastoma, hepatocellular carcinoma, Hodgkin lymphoma, Kaposi's sarcoma, leukemia, lung carcinoma, leiomyosarcoma, laryngeal squamous cell carcinoma, melanoma, mucosa-associated lymphoid tissue B-cell lymphoma, medulloblastoma, mantle cell lymphoma, myeloid leukemia, multiple myeloma, high-risk myelodysplastic syndrome, mesothelioma, neurofibroma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, Schwanomma, small cell lung cancer, salivary gland tumor, sporadic papillary renal carcinoma, thyroid carcinoma, testicular tumor, and/or urothelial carcinoma.

In yet further aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-126 or miR-126 inhibitor are administered to patients with astrocytoma, acute myeloid leukemia, breast carcinoma, Burkitt's lymphoma, bladder carcinoma, cervical carcinoma, colorectal carcinoma, endometrial carcinoma, Ewing's sarcoma, glioma, glioblastoma, gastric carcinoma, gastrinoma, hepatoblastoma, hepatocellular carcinoma, Hodgkin lymphoma, leukemia, lung carcinoma, melanoma, mantle cell lymphoma, myeloid leukemia, mesothelioma, neurofibroma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, Schwanomma, small cell lung cancer, sporadic papillary renal carcinoma, and/or thyroid carcinoma.

In a further aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-143 or miR-143 inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal

carcinoma, endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, leukemia, lung carcinoma, melanoma, medulloblastoma, mantle cell lymphoma, multiple myeloma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, small cell lung cancer, thyroid carcinoma, and/or testicular tumor.

In still a further aspect, miR-15, miR-26, miR-31, miR-145, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31, miR-145, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-147 or miR-147 inhibitor are administered to patients with astrocytoma, breast carcinoma, bladder carcinoma, cervical carcinoma, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, leukemia, lipoma, melanoma, mantle cell lymphoma, myxofibrosarcoma, multiple myeloma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, and/or thyroid carcinoma.

In yet another aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31, miR-145, miR-147, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-188 or miR-188 inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute myeloid leukemia, breast carcinoma, B-cell lymphoma, Burkitt's lymphoma, bladder carcinoma, cervical carcinoma, chronic lymphoblastic leukemia, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, leukemia, lung carcinoma, melanoma, multiple myeloma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, pancreatic carcinoma, prostate carcinoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, thyroid carcinoma, and/or testicular tumor.

In other aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31,

miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-200 or miR-200 inhibitor are administered to patients with anaplastic large cell lymphoma, breast carcinoma, B-cell lymphoma, cervical carcinoma, chronic lymphoblastic leukemia, colorectal carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, leukemia, lung carcinoma, lipoma, multiple myeloma, mesothelioma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, thyroid carcinoma, and/or testicular tumor

In other aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-216, miR-331, or mmu-miR-292-3p, or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-216, miR-331, or mmu-miR-292-3p inhibitor and miR-215 or miR-215 inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, chronic lymphoblastic leukemia, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, esophageal squamous cell carcinoma, Ewing's sarcoma, glioma, glioblastoma, gastric carcinoma, gastrinoma, hepatoblastoma, hepatocellular carcinoma, Hodgkin lymphoma, Kaposi's sarcoma, leukemia, lung carcinoma, lipoma, leiomyosarcoma, liposarcoma, melanoma, mucosa-associated lymphoid tissue B-cell lymphoma, mantle cell lymphoma, myxofibrosarcoma, myeloid leukemia, multiple myeloma, neuroblastoma, neurofibroma, non-Hodgkin lymphoma, nasopharyngeal carcinoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, Schwanomma, small cell lung cancer, thyroid carcinoma, testicular tumor, urothelial carcinoma, and/or Wilm's tumor.

In certain aspects, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-331, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-331, or mmu-miR-292-3p inhibitor and miR-216 or miR-216 inhibitor are administered to patients with astrocytoma, breast carcinoma, cervical carcinoma, carcinoma of the head and neck, colorectal carcinoma,

endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, leukemia, lung carcinoma, mucosa-associated lymphoid tissue B-cell lymphoma, myeloid leukemia, neurofibroma, non-Hodgkin lymphoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, prostate carcinoma, pheochromocytoma, squamous cell carcinoma of the head and neck, and/or testicular tumor.

In a further aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or miR-331, or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or miR-331 inhibitor and miR-292-3p or miR-292-3p inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, chronic myeloid leukemia, colorectal carcinoma, endometrial carcinoma, Ewing's sarcoma, glioma, glioblastoma, gastric carcinoma, hepatoblastoma, hepatocellular carcinoma, Kaposi's sarcoma, leukemia, lung carcinoma, lipoma, leiomyosarcoma, liposarcoma, laryngeal squamous cell carcinoma, melanoma, myxofibrosarcoma, multiple myeloma, neuroblastoma, non-Hodgkin lymphoma, nasopharyngeal carcinoma, non-small cell lung carcinoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, Schwanomma, small cell lung cancer, thyroid carcinoma, testicular tumor, urothelial carcinoma, and/or Wilm's tumor.

In still a further aspect, miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or mmu-miR-292-3p or miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or mmu-miR-292-3p inhibitor and miR-331 or miR-331 inhibitor are administered to patients with astrocytoma, anaplastic large cell lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, angiosarcoma, breast carcinoma, B-cell lymphoma, bladder carcinoma, cervical carcinoma, carcinoma of the head and neck, chronic lymphoblastic leukemia, colorectal carcinoma, endometrial carcinoma, glioma, glioblastoma, gastric carcinoma, gastrinoma, hepatocellular carcinoma, Kaposi's sarcoma, leukemia, lung carcinoma, leiomyosarcoma, laryngeal squamous cell carcinoma, larynx carcinoma, melanoma, myxofibrosarcoma, myeloid leukemia, multiple myeloma, neuroblastoma,

neurofibroma, non-Hodgkin lymphoma, ovarian carcinoma, oesophageal carcinoma, osteosarcoma, pancreatic carcinoma, prostate carcinoma, pheochromocytoma, renal cell carcinoma, rhabdomyosarcoma, squamous cell carcinoma of the head and neck, small cell lung cancer, thyroid carcinoma, and/or testicular tumor.

It is contemplated that when miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p or a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p inhibitor is given in combination with one or more other miRNA molecules, the multiple different miRNAs or inhibitors may be given at the same time or sequentially. In some embodiments, therapy proceeds with one miRNA or inhibitor and that therapy is followed up with therapy with the other miRNA or inhibitor 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 minutes, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 hours, 1, 2, 3, 4, 5, 6, 7 days, 1, 2, 3, 4, 5 weeks, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or any such combination later.

Further embodiments include the identification and assessment of an expression profile indicative of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p status in a cell or tissue comprising expression assessment of one or more gene from Table 1, 3, and/or 4, or any combination thereof.

In some embodiments, it may be useful to know whether a cell expresses a particular miRNA endogenously or whether such expression is affected under particular conditions or when it is in a particular disease state. Thus, in some embodiments of the invention, methods include assaying a cell or a sample containing a cell for the presence of one or more miRNA marker gene or mRNA or other analyte indicative of the expression level of a gene of interest. Consequently, in some embodiments, methods include a step of generating an RNA profile for a sample. The term "RNA profile" or "gene expression profile" refers to a set of data regarding the expression pattern for one or more gene or genetic marker in the sample (*e.g.*, a plurality of nucleic acid probes that identify one or more markers or genes from Tables 1, 3, and/or 4); it is contemplated that the nucleic acid profile can be obtained using a set of RNAs, using for example nucleic acid amplification or hybridization

techniques well know to one of ordinary skill in the art. The difference in the expression profile in the sample from a patient and a reference expression profile, such as an expression profile from a normal or non-pathologic sample, or a digitized reference, is indicative of a pathologic, disease, or cancerous condition. In certain aspects the expression profile is an indicator of a propensity to or probability of (*i.e.*, risk factor for a disease or condition) developing such a condition(s). Such a risk or propensity may indicate a treatment, increased monitoring, prophylactic measures, and the like. A nucleic acid or probe set may comprise or identify a segment of a corresponding mRNA and may include all or part of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 ,13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 100, 200, 500, or more segments, including any integer or range derivable there between, of a gene or genetic marker, or a nucleic acid, mRNA or a probe representative thereof that is listed in Tables 1, 3, and/or 4 or identified by the methods described herein.

Certain embodiments of the invention are directed to compositions and methods for assessing, prognosing, or treating a pathological condition in a patient comprising measuring or determining an expression profile of one or more miRNA or marker(s) in a sample from the patient, wherein a difference in the expression profile in the sample from the patient and an expression profile of a normal sample or reference expression profile is indicative of pathological condition and particularly cancer (*e.g.*, In certain aspects of the invention, the miRNAs, cellular pathway, gene, or genetic marker is or is representative of one or more pathway or marker described in Table 1, 2, 3, and/or 4, including any combination thereof.

Aspects of the invention include diagnosing, assessing, or treating a pathologic condition or preventing a pathologic condition from manifesting. For example, the methods can be used to screen for a pathological condition; assess prognosis of a pathological condition; stage a pathological condition; assess response of a pathological condition to therapy; or to modulate the expression of a gene, genes, or related pathway as a first therapy or to render a subject sensitive or more responsive to a second therapy. In particular aspects, assessing the pathological condition of the patient can be assessing prognosis of the patient. Prognosis may include, but is not

limited to an estimation of the time or expected time of survival, assessment of response to a therapy, and the like. In certain aspects, the altered expression of one or more gene or marker is prognostic for a patient having a pathologic condition, wherein the marker is one or more of markers in Table 1, 3, and/or 4, including any combination thereof.

Certain embodiments of the invention include determining expression of one or more marker, gene, or nucleic acid segment representative of one or more genes, by using an amplification assay, a hybridization assay, or protein assay, a variety of which are well known to one of ordinary skill in the art. In certain aspects, an amplification assay can be a quantitative amplification assay, such as quantitative RT-PCR or the like. In still further aspects, a hybridization assay can include array hybridization assays or solution hybridization assays. The nucleic acids from a sample may be labeled from the sample and/or hybridizing the labeled nucleic acid to one or more nucleic acid probes. Nucleic acids, mRNA, and/or nucleic acid probes may be coupled to a support. Such supports are well known to those of ordinary skill in the art and include, but are not limited to glass, plastic, metal, or latex. In particular aspects of the invention, the support can be planar or in the form of a bead or other geometric shapes or configurations known in the art. Proteins are typically assayed by immunoblotting, chromatography, or mass spectrometry or other methods known to those of ordinary skill in the art.

The present invention also concerns kits containing compositions of the invention or compositions to implement methods of the invention. In some embodiments, kits can be used to evaluate one or more marker molecules, and/or express one or more miRNA or miRNA inhibitor. In certain embodiments, a kit contains, contains at least or contains at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 100, 150, 200 or more probes, recombinant nucleic acid, or synthetic nucleic acid molecules related to the markers to be assessed or an miRNA or miRNA inhibitor to be expressed or modulated, and may include any range or combination derivable therein. Kits may comprise components, which may be individually packaged or placed in a container, such as a tube, bottle, vial, syringe, or other suitable container

means. Individual components may also be provided in a kit in concentrated amounts; in some embodiments, a component is provided individually in the same concentration as it would be in a solution with other components. Concentrations of components may be provided as 1x, 2x, 5x, 10x, or 20x or more. Kits for using probes, synthetic nucleic acids, recombinant nucleic acids, or non-synthetic nucleic acids of the invention for therapeutic, prognostic, or diagnostic applications are included as part of the invention. Specifically contemplated are any such molecules corresponding to any miRNA reported to influence biological activity or expression of one or more marker gene or gene pathway described herein. In certain aspects, negative and/or positive controls are included in some kit embodiments. The control molecules can be used to verify transfection efficiency and/or control for transfection-induced changes in cells.

Certain embodiments are directed to a kit for assessment of a pathological condition or the risk of developing a pathological condition in a patient by nucleic acid profiling of a sample comprising, in suitable container means, two or more nucleic acid hybridization or amplification reagents. The kit can comprise reagents for labeling nucleic acids in a sample and/or nucleic acid hybridization reagents. The hybridization reagents typically comprise hybridization probes. Amplification reagents include, but are not limited to amplification primers, reagents, and enzymes.

In some embodiments of the invention, an expression profile is generated by steps that include: (a) labeling nucleic acid in the sample; (b) hybridizing the nucleic acid to a number of probes, or amplifying a number of nucleic acids, and (c) determining and/or quantitating nucleic acid hybridization to the probes or detecting and quantitating amplification products, wherein an expression profile is generated. See U.S. Provisional Patent Application 60/575,743 and the U.S. Provisional Patent Application 60/649,584, and U.S. Patent Application Serial No. 11/141,707 and U.S. Patent Application Serial No. 11/273,640, all of which are hereby incorporated by reference.

Methods of the invention involve diagnosing and/or assessing the prognosis of a patient based on a miRNA and/or a marker nucleic acid expression profile. In certain embodiments, the elevation or reduction in the level of expression of a particular gene or genetic pathway or set of nucleic acids in a cell is correlated with a

disease state or pathological condition compared to the expression level of the same in a normal or non-pathologic cell or tissue sample. This correlation allows for diagnostic and/or prognostic methods to be carried out when the expression level of one or more nucleic acid is measured in a biological sample being assessed and then compared to the expression level of a normal or non-pathologic cell or tissue sample. It is specifically contemplated that expression profiles for patients, particularly those suspected of having or having a propensity for a particular disease or condition such as cancer, can be generated by evaluating any of or sets of the miRNAs and/or nucleic acids discussed in this application. The expression profile that is generated from the patient will be one that provides information regarding the particular disease or condition. In many embodiments, the profile is generated using nucleic acid hybridization or amplification, (*e.g.*, array hybridization or RT-PCR). In certain aspects, an expression profile can be used in conjunction with other diagnostic and/or prognostic tests, such as histology, protein profiles in the serum and/or cytogenetic assessment.

Table 2A. Significantly affected functional cellular pathways following hsa-miR-15 over-expression in human cancer cells.

Number of Genes	Pathway Functions
18	Cancer, Tumor Morphology, Cellular Growth and Proliferation
16	Cell Cycle, Cancer, Skeletal and Muscular Disorders
15	Cellular Movement, Cellular Assembly and Organization, Cellular Compromise
15	Inflammatory Disease, Cell Morphology, Dermatological Diseases and Conditions
15	Cellular Movement, Cell-To-Cell Signaling and Interaction, Tissue Development
5	Cardiovascular System Development and Function, Gene Expression, Cancer
1	Cancer, Cell Morphology, Cell-To-Cell Signaling and Interaction
1	Cancer, Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction
1	Cancer, Cell Cycle, Cellular Movement
1	Cellular Assembly and Organization, Neurological Disease, Psychological Disorders
1	Cell Death, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation
1	Cell-To-Cell Signaling and Interaction, Cellular Development, Connective Tissue Development and Function
1	Cellular Assembly and Organization, Cell Morphology, Molecular Transport

Table 2B. Significantly affected functional cellular pathways following hsa-miR-26 over-expression in human cancer cells.

Number of Genes	Pathway Functions

18	Cellular Movement, Cancer, Cell Death
16	Cellular Development, Cellular Growth and Proliferation, Connective Tissue Development and Function
16	Cellular Movement, Cellular Growth and Proliferation, Cardiovascular System Development and Function
15	Cell Signaling, Cancer, Molecular Transport
14	Cell Morphology, Digestive System Development and Function, Renal and Urological System Development and Function
14	Carbohydrate Metabolism, Cell Signaling, Energy Production
14	Cell Signaling, Gene Expression, Cellular Growth and Proliferation
13	Cancer, Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization
12	Cell Death, Cancer, Cellular Movement
1	Cancer, Drug Metabolism, Genetic Disorder
1	Cellular Assembly and Organization, RNA Post-Transcriptional Modification
1	Molecular Transport, Protein Trafficking, Cell-To-Cell Signaling and Interaction

Table 2C. Significantly affected functional cellular pathways following inhibition of hsa-miR-31 expression in human cancer cells.

Number of Genes	Pathway Functions
5	Hematological System Development and Function, Immune Response, Immune and Lymphatic System Development and Function

Table 2D. Significantly affected functional cellular pathways following hsa-miR-145 over-expression in human cancer cells.

Number of Genes	Pathway Functions
1	Cancer, Cell Morphology, Dermatological Diseases and Conditions
1	Tissue Morphology, Hematological System Development and Function, Immune and Lymphatic System Development and Function

Table 2E. Significantly affected functional cellular pathways following hsa-miR-147 over-expression in human cancer cells.

Number of Genes	Pathway Functions
16	Cardiovascular System Development and Function, Cellular Movement, Cellular Growth and Proliferation
15	Cancer, Cell Morphology, Dermatological Diseases and Conditions
15	Cellular Assembly and Organization, Cardiovascular Disease, Cell Death
14	Cellular Movement, Renal and Urological System Development and Function, Cancer
14	Hematological Disease, Cellular Growth and Proliferation, Lipid Metabolism
12	Cellular Compromise, Immune Response, Cancer
7	Cell Morphology, Cellular Development, Cell-To-Cell Signaling and

	Interaction
1	Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization, Nervous System Development and Function
1	Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Connective Tissue Development and Function
1	Cellular Assembly and Organization, Cellular Function and Maintenance, Cell-To-Cell Signaling and Interaction

Table 2F. Significantly affected functional cellular pathways following hsa-miR-188 over-expression in human cancer cells.

Number of Genes	Pathway Functions
15	Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction, Tissue Development
14	Tissue Development, Cell Death, Renal and Urological Disease
13	Cell Cycle, Cellular Growth and Proliferation, Endocrine System Development and Function
8	Cell Death, DNA Replication, Recombination, and Repair, Cellular Growth and Proliferation
1	Cell Morphology, Cellular Assembly and Organization, Psychological Disorders
1	Cell Cycle, Dermatological Diseases and Conditions, Genetic Disorder
1	Amino Acid Metabolism, Post-Translational Modification, Small Molecule Biochemistry
1	Molecular Transport, Protein Trafficking, Cell-To-Cell Signaling and Interaction

Table 2G. Significantly affected functional cellular pathways following hsa-miR-215 over-expression in human cancer cells.

Number of Genes	Pathway Functions
21	Cellular Growth and Proliferation, Cell Death, Lipid Metabolism
16	Cellular Function and Maintenance, Hematological System Development and Function, Immune and Lymphatic System Development and Function
15	Cell Death, Cancer, Connective Tissue Disorders
14	Cellular Growth and Proliferation, Connective Tissue Development and Function, Cellular Assembly and Organization
13	Cancer, Cell Cycle, Reproductive System Disease
13	Cellular Growth and Proliferation, Cell Death, Hematological System Development and Function
11	Cancer, Gene Expression, Cardiovascular Disease
1	Neurological Disease, Skeletal and Muscular Disorders, Cellular Function and Maintenance
1	Cardiovascular System Development and Function, Cell Morphology, Cellular Development
1	Cell Death, Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation
1	Hematological Disease, Genetic Disorder, Hematological System Development and Function

Table 2H. Significantly affected functional cellular pathways following hsa-miR-216 over-expression in human cancer cells.

Number of Genes	Pathway Functions
14	Molecular Transport, Small Molecule Biochemistry, Cellular Development
13	Gene Expression, Cellular Growth and Proliferation, Connective Tissue Development and Function
5	Cell Death, DNA Replication, Recombination, and Repair, Cancer
1	Cell-To-Cell Signaling and Interaction, Cellular Function and Maintenance, Connective Tissue Development and Function

Table 2I. Significantly affected functional cellular pathways following hsa-miR-331 over-expression in human cancer cells.

Number of Genes	Pathway Functions
13	Cell Death, Dermatological Diseases and Conditions, Cancer
12	Developmental Disorder, Cancer, Cell Death
11	Cancer, Cardiovascular Disease, Cell Morphology
8	Cell Signaling, Gene Expression, Cancer
1	Behavior, Connective Tissue Development and Function, Developmental Disorder
1	Cancer, Hair and Skin Development and Function, Nervous System Development and Function
1	Cellular Function and Maintenance
1	Lipid Metabolism, Small Molecule Biochemistry, Cancer
1	Molecular Transport, Protein Trafficking, Cell-To-Cell Signaling and Interaction
1	Cellular Assembly and Organization, Cell Morphology, Molecular Transport
1	Cell Cycle, Cellular Movement, Cell Morphology
1	Cell Signaling, Neurological Disease, Cell Morphology

Table 2J. Significantly affected functional cellular pathways following mmu-miR-292-3p over-expression in human cancer cells.

Number of Genes	Pathway Functions
35	Cellular Growth and Proliferation, Cancer, Cell Death
21	DNA Replication, Recombination, and Repair, Cellular Growth and Proliferation, Lipid Metabolism
18	Cancer, Cell Death, Connective Tissue Disorders
17	DNA Replication, Recombination, and Repair, Cellular Function and Maintenance, Cell-To-Cell Signaling and Interaction
17	Gene Expression, Cancer, Connective Tissue Disorders
15	Cellular Assembly and Organization, Nervous System Development and Function, Cellular Movement
14	Cell Morphology, Cancer, Cell Death
14	Cell Morphology, Renal and Urological System Development and Function, Cancer
13	Cellular Assembly and Organization, Cellular Compromise, Gene Expression
5	Gene Expression, Lipid Metabolism, Small Molecule Biochemistry
1	Gene Expression
1	Reproductive System Development and Function, Cell-To-Cell Signaling and Interaction
1	

1	Cancer, Cardiovascular System Development and Function, Cell-To-Cell Signaling and Interaction
1	Cellular Function and Maintenance
1	Post-Translational Modification, Gene Expression, Protein Synthesis
1	Nervous System Development and Function, Nucleic Acid Metabolism, Cellular Movement
1	Genetic Disorder, Metabolic Disease, Cellular Assembly and Organization
1	Lipid Metabolism, Small Molecule Biochemistry, Cellular Development

Table 3A. Predicted hsa-miR-15 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-15.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al*, 2005)	Description
ABCA1	NM_005502	ATP-binding cassette, sub-family A member 1
ADARB1	NM_001033049	RNA-specific adenosine deaminase B1 isoform 4
ADRB2	NM_000024	adrenergic, beta-2-, receptor, surface
AKAP12	NM_005100	A-kinase anchor protein 12 isoform 1
ANKRD46	NM_198401	ankyrin repeat domain 46
AP1S2	NM_003916	adaptor-related protein complex 1 sigma 2
ARHGDIA	NM_004309	Rho GDP dissociation inhibitor (GDI) alpha
ARL2	NM_001667	ADP-ribosylation factor-like 2
BAG5	NM_001015048	BCL2-associated athanogene 5 isoform b
CA12	NM_001218	carbonic anhydrase XII isoform 1 precursor
CCND1	NM_053056	cyclin D1
CCND3	NM_001760	cyclin D3
CDC37L1	NM_017913	cell division cycle 37 homolog (S.
CDCA4	NM_017955	cell division cycle associated 4
CDS2	NM_003818	phosphatidate cytidylyltransferase 2
CGI-38	NM_015964	hypothetical protein LOC51673
CHUK	NM_001278	conserved helix-loop-helix ubiquitous kinase
COL6A1	NM_001848	collagen, type VI, alpha 1 precursor
CYP4F3	NM_000896	cytochrome P450, family 4, subfamily F,
DDAH1	NM_012137	dimethylarginine dimethylaminohydrolase 1
DUSP6	NM_001946	dual specificity phosphatase 6 isoform a
EIF4E	NM_001968	eukaryotic translation initiation factor 4E
FAM18B	NM_016078	hypothetical protein LOC51030
FGF2	NM_002006	fibroblast growth factor 2
FGFR4	NM_002011	fibroblast growth factor receptor 4 isoform 1
FKBP1B	NM_004116	FK506-binding protein 1B isoform a
FSTL1	NM_007085	follistatin-like 1 precursor
GCLC	NM_001498	glutamate-cysteine ligase, catalytic subunit
GFPT1	NM_002056	glucosamine-fructose-6-phosphate
GTSE1	NM_016426	G-2 and S-phase expressed 1
HAS2	NM_005328	hyaluronan synthase 2
HMGA2	NM_001015886	high mobility group AT-hook 2 isoform c
HSPA1B	NM_005346	heat shock 70kDa protein 1B
IGFBP3	NM_000598	insulin-like growth factor binding protein 3
KCNJ2	NM_000891	potassium inwardly-rectifying channel J2
LCN2	NM_005564	lipocalin 2 (oncogene 24p3)
LOXL2	NM_002318	lysyl oxidase-like 2 precursor
LRP12	NM_013437	suppression of tumorigenicity

MAP7	NM_003980	microtubule-associated protein 7
NTE	NM_006702	neuropathy target esterase
PLSCR4	NM_020353	phospholipid scramblase 4
PODXL	NM_001018111	podocalyxin-like precursor isoform 1
PPP1R11	NM_021959	protein phosphatase 1, regulatory (inhibitor)
QKI	NM_206853	quaking homolog, KH domain RNA binding isoform
RAFTLIN	NM_015150	raft-linking protein
RPS6KA3	NM_004586	ribosomal protein S6 kinase, 90kDa, polypeptide
RPS6KA5	NM_004755	ribosomal protein S6 kinase, 90kDa, polypeptide
SLC11A2	NM_000617	solute carrier family 11 (proton-coupled
SLC26A2	NM_000112	solute carrier family 26 member 2
SNAP23	NM_003825	synaptosomal-associated protein 23 isoform
SPARC	NM_003118	secreted protein, acidic, cysteine-rich
SPFH2	NM_007175	SPFH domain family, member 2 isoform 1
STC1	NM_003155	stanniocalcin 1 precursor
SYNE1	NM_015293	nesprin 1 isoform beta
TACC1	NM_006283	transforming, acidic coiled-coil containing
TAF15	NM_003487	TBP-associated factor 15 isoform 2
TFG	NM_001007565	TRK-fused gene
THUMPD1	NM_017736	THUMP domain containing 1
TNFSF9	NM_003811	tumor necrosis factor (ligand) superfamily,
TPM1	NM_001018004	tropomyosin 1 alpha chain isoform 3
UBE2I	NM_003345	ubiquitin-conjugating enzyme E2I
VIL2	NM_003379	villin 2
VTI1B	NM_006370	vesicle transport through interaction with
YRDC	NM_024640	ischemia/reperfusion inducible protein

Table 3B. Predicted hsa-miR-26 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-26.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**Description**
ABR	NM_001092	active breakpoint cluster region-related
ALDH5A1	NM_001080	aldehyde dehydrogenase 5A1 precursor, isoform 2
ATP9A	NM_006045	ATPase, Class II, type 9A
B4GALT4	NM_003778	UDP-Gal:betaGlcNAc beta 1,4-
BCAT1	NM_005504	branched chain aminotransferase 1, cytosolic
C14orf10	NM_017917	chromosome 14 open reading frame 10
C1orf116	NM_023938	specifically androgen-regulated protein
C8orf1	NM_004337	hypothetical protein LOC734
CCDC28A	NM_015439	hypothetical protein LOC25901
CDH4	NM_001794	cadherin 4, type 1 preproprotein
CDK8	NM_001260	cyclin-dependent kinase 8
CHAF1A	NM_005483	chromatin assembly factor 1, subunit A (p150)
CHORDC1	NM_012124	cysteine and histidine-rich domain
CLDN3	NM_001306	claudin 3
CREBL2	NM_001310	cAMP responsive element binding protein-like 2
CTGF	NM_001901	connective tissue growth factor
EFEMP1	NM_004105	EGF-containing fibulin-like extracellular matrix
EHD1	NM_006795	EH-domain containing 1
EIF2S1	NM_004094	eukaryotic translation initiation factor 2,

EPHA2	NM_004431	ephrin receptor EphA2
FBXO11	NM_025133	F-box only protein 11 isoform 1
GALC	NM_000153	galactosylceramidase isoform a precursor
GMDS	NM_001500	GDP-mannose 4,6-dehydratase
GRB10	NM_001001549	growth factor receptor-bound protein 10 isoform
HAS2	NM_005328	hyaluronan synthase 2
HECTD3	NM_024602	HECT domain containing 3
HES1	NM_005524	hairy and enhancer of split 1
HMGA1	NM_002131	high mobility group AT-hook 1 isoform b
HMGA2	NM_001015886	high mobility group AT-hook 2 isoform c
HNMT	NM_001024074	histamine N-methyltransferase isoform 2
KIAA0152	NM_014730	hypothetical protein LOC9761
LOC153561	NM_207331	hypothetical protein LOC153561
MAPK6	NM_002748	mitogen-activated protein kinase 6
MCL1	NM_021960	myeloid cell leukemia sequence 1 isoform 1
METAP2	NM_006838	methionyl aminopeptidase 2
MYCBP	NM_012333	c-myc binding protein
NAB1	NM_005966	NGFI-A binding protein 1
NR5A2	NM_003822	nuclear receptor subfamily 5, group A, member 2
NRG1	NM_013958	neuregulin 1 isoform HRG-beta3
NRIP1	NM_003489	receptor interacting protein 140
PAPPA	NM_002581	pregnancy-associated plasma protein A
PDCD4	NM_014456	programmed cell death 4 isoform 1
PHACTR2	NM_014721	phosphatase and actin regulator 2
PTK9	NM_002822	twinfilin isoform 1
RAB11FIP1	NM_001002233	Rab coupling protein isoform 2
RAB21	NM_014999	RAB21, member RAS oncogene family
RECK	NM_021111	RECK protein precursor
RHOQ	NM_012249	ras-like protein TC10
SC4MOL	NM_001017369	sterol-C4-methyl oxidase-like isoform 2
SLC26A2	NM_000112	solute carrier family 26 member 2
SLC2A3	NM_006931	solute carrier family 2 (facilitated glucose
SRD5A1	NM_001047	steroid-5-alpha-reductase 1
STK39	NM_013233	serine threonine kinase 39 (STE20/SPS1 homolog,
TIMM17A	NM_006335	translocase of inner mitochondrial membrane 17
TRAPPC4	NM_016146	trafficking protein particle complex 4
ULK1	NM_003565	unc-51-like kinase 1
UQCRB	NM_006294	ubiquinol-cytochrome c reductase binding
ZNF259	NM_003904	zinc finger protein 259

Table 3C. Predicted hsa-miR-31 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-31.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	**$\Delta \log_2$**
AKAP2 /// PALM2-AKAP2	NM_001004065 /// NM_007203 /// NM_147150	0.881687
CXCL3	NM_002090	0.800224
IL8	NM_000584	1.54253
MAFF	NM_012323 /// NM_152878	0.873461
QKI	NM_006775 /// NM_206853 /// NM_206854 /// NM_206855	0.773843
SLC26A2	NM_000112	0.784073

STC1	NM_003155	0.904092

Table 3D. Predicted hsa-miR-145 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-145.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	Description
CXCL3	NM_002090	chemokine (C-X-C motif) ligand 3

Table 3E. Predicted hsa-miR-147 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-147.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	Description
ANK3	NM_001149	ankyrin 3 isoform 2
ANTXR1	NM_032208	tumor endothelial marker 8 isoform 1 precursor
ARID5B	NM_032199	AT rich interactive domain 5B (MRF1-like)
ATP9A	NM_006045	ATPase, Class II, type 9A
B4GALT1	NM_001497	UDP-Gal:betaGlcNAc beta 1,4-
C1orf24	NM_052966	niban protein isoform 2
C21orf25	NM_199050	hypothetical protein LOC25966
C6orf120	NM_001029863	hypothetical protein LOC387263
CCND1	NM_053056	cyclin D1
COL4A2	NM_001846	alpha 2 type IV collagen preproprotein
DCP2	NM_152624	DCP2 decapping enzyme
DPYSL4	NM_006426	dihydropyrimidinase-like 4
EIF2C1	NM_012199	eukaryotic translation initiation factor 2C, 1
ETS2	NM_005239	v-ets erythroblastosis virus E26 oncogene
F2RL1	NM_005242	coagulation factor II (thrombin) receptor-like 1
FYCO1	NM_024513	FYVE and coiled-coil domain containing 1
FZD7	NM_003507	frizzled 7
GLUL	NM_001033044	glutamine synthetase
GNS	NM_002076	glucosamine (N-acetyl)-6-sulfatase precursor
GOLPH2	NM_016548	golgi phosphoprotein 2
GYG2	NM_003918	glycogenin 2
HAS2	NM_005328	hyaluronan synthase 2
HIC2	NM_015094	hypermethylated in cancer 2
KCNMA1	NM_001014797	large conductance calcium-activated potassium
LHFP	NM_005780	lipoma HMGIC fusion partner
LIMK1	NM_002314	LIM domain kinase 1
MAP3K2	NM_006609	mitogen-activated protein kinase kinase kinase
MICAL2	NM_014632	microtubule associated monoxygenase, calponin
NAV3	NM_014903	neuron navigator 3
NPTX1	NM_002522	neuronal pentraxin I precursor
NUPL1	NM_001008564	nucleoporin like 1 isoform b
OLR1	NM_002543	oxidised low density lipoprotein (lectin-like)
OXTR	NM_000916	oxytocin receptor
PDCD4	NM_014456	programmed cell death 4 isoform 1
PLAU	NM_002658	urokinase plasminogen activator preproprotein
PTHLH	NM_002820	parathyroid hormone-like hormone isoform 2
RAB22A	NM_020673	RAS-related protein RAB-22A
RHOC	NM_175744	ras homolog gene family, member C
SPARC	NM_003118	secreted protein, acidic, cysteine-rich

STC1	NM_003155	stanniocalcin 1 precursor
TGFBR2	NM_001024847	TGF-beta type II receptor isoform A precursor
TM4SF20	NM_024795	transmembrane 4 L six family member 20
TNFRSF12A	NM_016639	type I transmembrane protein Fn14
ULK1	NM_003565	unc-51-like kinase 1

Table 3F. Predicted hsa-miR-188 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-188.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	Description
ANKFY1	NM_016376	ankyrin repeat and FYVE domain containing 1
ANKRD46	NM_198401	ankyrin repeat domain 46
ANTXR1	NM_018153	tumor endothelial marker 8 isoform 3 precursor
ATXN1	NM_000332	ataxin 1
AXL	NM_001699	AXL receptor tyrosine kinase isoform 2
BPGM	NM_001724	2,3-bisphosphoglycerate mutase
C6orf120	NM_001029863	hypothetical protein LOC387263
C8orf1	NM_004337	hypothetical protein LOC734
CBFB	NM_001755	core-binding factor, beta subunit isoform 2
CCDC6	NM_005436	coiled-coil domain containing 6
CD2AP	NM_012120	CD2-associated protein
CDK2AP1	NM_004642	CDK2-associated protein 1
CLU	NM_001831	clusterin isoform 1
CREB3L2	NM_194071	cAMP responsive element binding protein 3-like
DAAM1	NM_014992	dishevelled-associated activator of
DCP2	NM_152624	DCP2 decapping enzyme
DKFZp564K142	NM_032121	implantation-associated protein
DLG5	NM_004747	discs large homolog 5
EDEM1	NM_014674	ER degradation enhancer, mannosidase alpha-like
ELOVL6	NM_024090	ELOVL family member 6, elongation of long chain
EMP1	NM_001423	epithelial membrane protein 1
ETS2	NM_005239	v-ets erythroblastosis virus E26 oncogene
FBXO11	NM_025133	F-box only protein 11 isoform 1
GATAD1	NM_021167	GATA zinc finger domain containing 1
GPR125	NM_145290	G protein-coupled receptor 125
GREM1	NM_013372	gremlin-1 precursor
HDAC3	NM_003883	histone deacetylase 3
HNRPA0	NM_006805	heterogeneous nuclear ribonucleoprotein A0
IER3IP1	NM_016097	immediate early response 3 interacting protein
IL13RA1	NM_001560	interleukin 13 receptor, alpha 1 precursor
ITGAV	NM_002210	integrin alpha-V precursor
M6PR	NM_002355	cation-dependent mannose-6-phosphate receptor
MAP4K5	NM_006575	mitogen-activated protein kinase kinase kinase
MARCKS	NM_002356	myristoylated alanine-rich protein kinase C
PALM2-AKAP2	NM_007203	PALM2-AKAP2 protein isoform 1
PCAF	NM_003884	p300/CBP-associated factor
PCTP	NM_021213	phosphatidylcholine transfer protein
PER2	NM_022817	period 2 isoform 1
PHACTR2	NM_014721	phosphatase and actin regulator 2
PLEKHA1	NM_001001974	pleckstrin homology domain containing, family A
PRKCA	NM_002737	protein kinase C, alpha

PTEN	NM_000314	phosphatase and tensin homolog
RGS20	NM_003702	regulator of G-protein signalling 20 isoform b
RNASE4	NM_002937	ribonuclease, RNase A family, 4 precursor
RSAD1	NM_018346	radical S-adenosyl methionine domain containing
SFRS7	NM_001031684	splicing factor, arginine/serine-rich 7, 35kDa
SLC39A9	NM_018375	solute carrier family 39 (zinc transporter),
SLC4A4	NM_003759	solute carrier family 4, sodium bicarbonate
ST13	NM_003932	heat shock 70kD protein binding protein
STC1	NM_003155	stanniocalcin 1 precursor
SUMO2	NM_001005849	SMT3 suppressor of mif two 3 homolog 2 isoform b
SYNJ2BP	NM_018373	synaptojanin 2 binding protein
TAPBP	NM_003190	tapasin isoform 1 precursor
TBL1X	NM_005647	transducin beta-like 1X
TMBIM1	NM_022152	transmembrane BAX inhibitor motif containing 1
TP73L	NM_003722	tumor protein p73-like
TRPC1	NM_003304	transient receptor potential cation channel,
VAV3	NM_006113	vav 3 oncogene
WDR39	NM_004804	WD repeat domain 39
ZNF281	NM_012482	zinc finger protein 281

Table 3G. Predicted hsa-miR-215 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-215.

Gene Symbol	**RefSeq Transcript ID** (Pruitt *et al.*, 2005)	Description
ABAT	NM_000663	4-aminobutyrate aminotransferase precursor
ACADSB	NM_001609	acyl-Coenzyme A dehydrogenase, short/branched
ADCY7	NM_001114	adenylate cyclase 7
APPBP2	NM_006380	amyloid beta precursor protein-binding protein
ARG2	NM_001172	arginase, type II precursor
ARL2BP	NM_012106	binder of Arl Two
ATP2B4	NM_001001396	plasma membrane calcium ATPase 4 isoform 4a
C1D	NM_006333	nuclear DNA-binding protein
C1orf116	NM_023938	specifically androgen-regulated protein
C1orf24	NM_052966	niban protein isoform 2
C6orf120	NM_001029863	hypothetical protein LOC387263
CDCA4	NM_017955	cell division cycle associated 4
CDCP1	NM_022842	CUB domain-containing protein 1 isoform 1
COL3A1	NM_000090	procollagen, type III, alpha 1
COL6A1	NM_001848	collagen, type VI, alpha 1 precursor
COPS7A	NM_016319	COP9 complex subunit 7a
CPM	NM_001005502	carboxypeptidase M precursor
CRSP2	NM_004229	cofactor required for Sp1 transcriptional
CTAGE5	NM_005930	CTAGE family, member 5 isoform 1
CTH	NM_001902	cystathionase isoform 1
CYP4F3	NM_000896	cytochrome P450, family 4, subfamily F,
DCAMKL1	NM_004734	doublecortin and CaM kinase-like 1
DICER1	NM_030621	dicer1
DKK3	NM_001018057	dickkopf homolog 3 precursor
DMN	NM_015286	desmuslin isoform B
EFEMP1	NM_004105	EGF-containing fibulin-like extracellular matrix
EREG	NM_001432	epiregulin precursor

FBLN1	NM_006487	fibulin 1 isoform A precursor
FGF2	NM_002006	fibroblast growth factor 2
FGFR1	NM_023107	fibroblast growth factor receptor 1 isoform 5
GREB1	NM_148903	GREB1 protein isoform c
HIC2	NM_015094	hypermethylated in cancer 2
HOXA10	NM_018951	homeobox A10 isoform a
HSA9761	NM_014473	dimethyladenosine transferase
IFIT1	NM_001548	interferon-induced protein with
IL11	NM_000641	interleukin 11 precursor
IL1R1	NM_000877	interleukin 1 receptor, type I precursor
IL6R	NM_000565	interleukin 6 receptor isoform 1 precursor
IL6ST	NM_175767	interleukin 6 signal transducer isoform 2
KIAA0256	NM_014701	hypothetical protein LOC9728
LAMC2	NM_005562	laminin, gamma 2 isoform a precursor
LMAN1	NM_005570	lectin, mannose-binding, 1 precursor
LNK	NM_005475	lymphocyte adaptor protein
LOC153561	NM_207331	hypothetical protein LOC153561
LOH3CR2A	NM_013343	loss of heterozygosity, 3, chromosomal region 2,
MAPKAPK2	NM_004759	mitogen-activated protein kinase-activated
MCM10	NM_018518	minichromosome maintenance protein 10 isoform 2
MCM3	NM_002388	minichromosome maintenance protein 3
NID1	NM_002508	nidogen (enactin)
NKTR	NM_001012651	natural killer-tumor recognition sequence
NMT2	NM_004808	glycylpeptide N-tetradecanoyltransferase 2
NRIP1	NM_003489	receptor interacting protein 140
NSF	NM_006178	N-ethylmaleimide-sensitive factor
NUDT15	NM_018283	nudix-type motif 15
PABPC4	NM_003819	poly A binding protein, cytoplasmic 4
PIP5K2B	NM_003559	phosphatidylinositol-4-phosphate 5-kinase type
PLAU	NM_002658	urokinase plasminogen activator preproprotein
PPP1CA	NM_001008709	protein phosphatase 1, catalytic subunit, alpha
PPP1CB	NM_002709	protein phosphatase 1, catalytic subunit, beta
PRNP	NM_000311	prion protein preproprotein
PTS	NM_000317	6-pyruvoyltetrahydropterin synthase
RAB2	NM_002865	RAB2, member RAS oncogene family
RAB40B	NM_006822	RAB40B, member RAS oncogene family
RASGRP1	NM_005739	RAS guanyl releasing protein 1
RB1	NM_000321	retinoblastoma 1
RNF141	NM_016422	ring finger protein 141
RPL4	NM_000968	ribosomal protein L4
SCEL	NM_003843	sciellin isoform a
SLC19A2	NM_006996	solute carrier family 19, member 2
SLC1A4	NM_003038	solute carrier family 1, member 4
SLC26A2	NM_000112	solute carrier family 26 member 2
SLC39A6	NM_012319	solute carrier family 39 (zinc transporter),
SMA4	NM_021652	SMA4
SMG1	NM_015092	PI-3-kinase-related kinase SMG-1
SOAT1	NM_003101	sterol O-acyltransferase (acyl-Coenzyme A:
SOD2	NM_000636	manganese superoxide dismutase isoform A
SPARC	NM_003118	secreted protein, acidic, cysteine-rich
SRD5A1	NM_001047	steroid-5-alpha-reductase 1
SS18	NM_001007559	synovial sarcoma translocation, chromosome 18

STC1	NM_003155	stanniocalcin 1 precursor
SULT1C1	NM_001056	sulfotransferase family, cytosolic, 1C, member 1
TBC1D16	NM_019020	TBC1 domain family, member 16
TDG	NM_001008411	thymine-DNA glycosylase isoform 2
TM4SF20	NM_024795	transmembrane 4 L six family member 20
TOP1	NM_003286	DNA topoisomerase I
TOR1AIP1	NM_015602	lamina-associated polypeptide 1B
TRIM22	NM_006074	tripartite motif-containing 22
TRIP13	NM_004237	thyroid hormone receptor interactor 13
WIG1	NM_022470	p53 target zinc finger protein isoform 1
ZFHX1B	NM_014795	zinc finger homeobox 1b
ZNF551	NM_138347	zinc finger protein 551
ZNF609	NM_015042	zinc finger protein 609

Table 3H. Predicted hsa-miR-216 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-216.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al*, 2005)	Description
AXL	NM_001699	AXL receptor tyrosine kinase isoform 2
BCL10	NM_003921	B-cell CLL/lymphoma 10
BNIP3L	NM_004331	BCL2/adenovirus E1B 19kD-interacting protein
CREB3L2	NM_194071	cAMP responsive element binding protein 3-like
CTH	NM_001902	cystathionase isoform 1
DIO2	NM_000793	deiodinase, iodothyronine, type II isoform a
EIF2S1	NM_004094	eukaryotic translation initiation factor 2,
FCHO1	NM_015122	FCH domain only 1
FEZ2	NM_005102	zygin 2
GREM1	NM_013372	gremlin-1 precursor
HDAC3	NM_003883	histone deacetylase 3
IDI1	NM_004508	isopentenyl-diphosphate delta isomerase
MGC4172	NM_024308	short-chain dehydrogenase/reductase
NFYC	NM_014223	nuclear transcription factor Y, gamma
PAPPA	NM_002581	pregnancy-associated plasma protein A
PIR	NM_001018109	pirin
PLEKHA1	NM_001001974	pleckstrin homology domain containing, family A
RP2	NM_006915	XRP2 protein
SCD	NM_005063	stearoyl-CoA desaturase
SLC2A3	NM_006931	solute carrier family 2 (facilitated glucose
SNRPD1	NM_006938	small nuclear ribonucleoprotein D1 polypeptide
SSB	NM_003142	autoantigen La
TEAD1	NM_021961	TEA domain family member 1
TGFBR3	NM_003243	transforming growth factor, beta receptor III
TIPRL	NM_152902	TIP41, TOR signalling pathway regulator-like
TMC5	NM_024780	transmembrane channel-like 5
UBE2V2	NM_003350	ubiquitin-conjugating enzyme E2 variant 2
VAV3	NM_006113	vav 3 oncogene
WIG1	NM_022470	p53 target zinc finger protein isoform 1

Table 3I. Predicted hsa-miR-331 targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR hsa-miR-331.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	Description
AQP3	NM_004925	aquaporin 3
B4GALT4	NM_003778	UDP-Gal:betaGlcNAc beta 1,4-
BCL2L1	NM_001191	BCL2-like 1 isoform 2
BICD2	NM_001003800	bicaudal D homolog 2 isoform 1
C19orf10	NM_019107	chromosome 19 open reading frame 10
CASP7	NM_033340	caspase 7 isoform beta
CDS2	NM_003818	phosphatidate cytidylyltransferase 2
COL4A2	NM_001846	alpha 2 type IV collagen preproprotein
COMMD9	NM_014186	COMM domain containing 9
CXCL1	NM_001511	chemokine (C-X-C motif) ligand 1
D15Wsu75e	NM_015704	hypothetical protein LOC27351
DDAH1	NM_012137	dimethylarginine dimethylaminohydrolase 1
EFNA1	NM_004428	ephrin A1 isoform a precursor
EHD1	NM_006795	EH-domain containing 1
EIF5A2	NM_020390	eIF-5A2 protein
ENO1	NM_001428	enolase 1
EREG	NM_001432	epiregulin precursor
FAM63B	NM_019092	hypothetical protein LOC54629
FGFR1	NM_000604	fibroblast growth factor receptor 1 isoform 1
GALNT7	NM_017423	polypeptide N-acetylgalactosaminyltransferase 7
HLRC1	NM_031304	HEAT-like (PBS lyase) repeat containing 1
IL13RA1	NM_001560	interleukin 13 receptor, alpha 1 precursor
IL32	NM_001012631	interleukin 32 isoform B
IL6R	NM_000565	interleukin 6 receptor isoform 1 precursor
ITGB4	NM_000213	integrin beta 4 isoform 1 precursor
KIAA0090	NM_015047	hypothetical protein LOC23065
KIAA1641	NM_020970	hypothetical protein LOC57730
MGC4172	NM_024308	short-chain dehydrogenase/reductase
NPTX1	NM_002522	neuronal pentraxin I precursor
NR5A2	NM_003822	nuclear receptor subfamily 5, group A, member 2
PDPK1	NM_002613	3-phosphoinositide dependent protein kinase-1
PHLPP	NM_194449	PH domain and leucine rich repeat protein
PLEC1	NM_000445	plectin 1 isoform 1
PODXL	NM_001018111	podocalyxin-like precursor isoform 1
PXN	NM_002859	Paxillin
RHOBTB1	NM_001032380	Rho-related BTB domain containing 1
RPA2	NM_002946	replication protein A2, 32kDa
RPE	NM_006916	ribulose-5-phosphate-3-epimerase isoform 2
SDC4	NM_002999	syndecan 4 precursor
SEPT9	NM_006640	septin 9
SLC7A1	NM_003045	solute carrier family 7 (cationic amino acid
STX6	NM_005819	syntaxin 6
TBC1D16	NM_019020	TBC1 domain family, member 16
THBS1	NM_003246	thrombospondin 1 precursor
TMEM2	NM_013390	transmembrane protein 2
TMEM45A	NM_018004	transmembrane protein 45A
TNC	NM_002160	tenascin C (hexabrachion)
TNFSF9	NM_003811	tumor necrosis factor (ligand) superfamily,
TRFP	NM_004275	Trf (TATA binding protein-related

TXLNA	NM_175852	Taxilin
USP46	NM_022832	ubiquitin specific protease 46
VANGL1	NM_138959	vang-like 1
WDR1	NM_005112	WD repeat-containing protein 1 isoform 2
WNT7B	NM_058238	wingless-type MMTV integration site family,
WSB2	NM_018639	WD SOCS-box protein 2
YRDC	NM_024640	ischemia/reperfusion inducible protein
ZNF259	NM_003904	zinc finger protein 259
ZNF395	NM_018660	zinc finger protein 395

Table 3J. Predicted mmu-miR-292-3p targets that exhibited altered mRNA expression levels in human cancer cells after transfection with pre-miR mmu-miR-292-3p.

Gene Symbol	RefSeq Transcript ID (Pruitt *et al.*, 2005)	Description
AP1G1	NM_001030007	adaptor-related protein complex 1, gamma 1
AKR7A2	NM_003689	aldo-keto reductase family 7, member A2
ALDH3A2	NM_000382	aldehyde dehydrogenase 3A2 isoform 2
ARCN1	NM_001655	Archain
ARL2BP	NM_012106	binder of Arl Two
BDKRB2	NM_000623	bradykinin receptor B2
BICD2	NM_001003800	bicaudal D homolog 2 isoform 1
BPGM	NM_001724	2,3-bisphosphoglycerate mutase
BRP44	NM_015415	brain protein 44
BTG2	NM_006763	B-cell translocation gene 2
C14orf2	NM_004894	hypothetical protein LOC9556
C1GALT1C1	NM_001011551	C1GALT1-specific chaperone 1
C2orf17	NM_024293	hypothetical protein LOC79137
CASP7	NM_033340	caspase 7 isoform beta
CDH4	NM_001794	cadherin 4, type 1 preproprotein
COPS6	NM_006833	COP9 signalosome subunit 6
COQ2	NM_015697	para-hydroxybenzoate-polyprenyltransferase,
CYP4F3	NM_000896	cytochrome P450, family 4, subfamily F,
DAZAP2	NM_014764	DAZ associated protein 2
DMN	NM_015286	desmuslin isoform B
DNAJB4	NM_007034	DnaJ (Hsp40) homolog, subfamily B, member 4
DPYSL4	NM_006426	dihydropyrimidinase-like 4
DTYMK	NM_012145	deoxythymidylate kinase (thymidylate kinase)
DUSP3	NM_004090	dual specificity phosphatase 3
EFNA1	NM_004428	ephrin A1 isoform a precursor
EIF2C1	NM_012199	eukaryotic translation initiation factor 2C, 1
FBLN1	NM_006486	fibulin 1 isoform D
FEZ2	NM_005102	zygin 2
FLJ13236	NM_024902	hypothetical protein FLJ13236
FLJ22662	NM_024829	hypothetical protein LOC79887
GALE	NM_000403	UDP-galactose-4-epimerase
GAS2L1	NM_152237	growth arrest-specific 2 like 1 isoform b
GCLC	NM_001498	glutamate-cysteine ligase, catalytic subunit
GLT25D1	NM_024656	glycosyltransferase 25 domain containing 1
GLUL	NM_001033044	glutamine synthetase

GMPR2	NM_001002000	guanosine monophosphate reductase 2 isoform 2
GNA13	NM_006572	guanine nucleotide binding protein (G protein),
GPI	NM_000175	glucose phosphate isomerase
GREB1	NM_033090	GREB1 protein isoform b
HBXIP	NM_006402	hepatitis B virus x-interacting protein
HIC2	NM_015094	hypermethylated in cancer 2
HMOX1	NM_002133	heme oxygenase (decyclizing) 1
ID1	NM_002165	inhibitor of DNA binding 1 isoform a
IGFBP3	NM_000598	insulin-like growth factor binding protein 3
INSIG1	NM_005542	insulin induced gene 1 isoform 1
IPO7	NM_006391	importin 7
KCNJ16	NM_018658	potassium inwardly-rectifying channel J16
LAMP1	NM_005561	lysosomal-associated membrane protein 1
LMO4	NM_006769	LIM domain only 4
LRP8	NM_001018054	low density lipoprotein receptor-related protein
MAPKAPK2	NM_004759	mitogen-activated protein kinase-activated
MCL1	NM_021960	myeloid cell leukemia sequence 1 isoform 1
NID1	NM_002508	nidogen (enactin)
NR2F2	NM_021005	nuclear receptor subfamily 2, group F, member 2
ORMDL2	NM_014182	ORMDL2
PAFAH1B2	NM_002572	platelet-activating factor acetylhydrolase,
PIGK	NM_005482	phosphatidylinositol glycan, class K precursor
PODXL	NM_001018111	podocalyxin-like precursor isoform 1
POLR3D	NM_001722	RNA polymerase III 53 kDa subunit RPC4
PON2	NM_000305	paraoxonase 2 isoform 1
PPAP2C	NM_003712	phosphatidic acid phosphatase type 2C isoform 1
PRDX6	NM_004905	peroxiredoxin 6
PREI3	NM_015387	preimplantation protein 3 isoform 1
PRNP	NM_000311	prion protein preproprotein
PSIP1	NM_033222	PC4 and SFRS1 interacting protein 1 isoform 2
PTER	NM_001001484	phosphotriesterase related
QKI	NM_006775	quaking homolog, KH domain RNA binding isoform
RAB13	NM_002870	RAB13, member RAS oncogene family
RAB32	NM_006834	RAB32, member RAS oncogene family
RAB4A	NM_004578	RAB4A, member RAS oncogene family
RNF141	NM_016422	ring finger protein 141
RRM2	NM_001034	ribonucleotide reductase M2 polypeptide
SDHA	NM_004168	succinate dehydrogenase complex, subunit A,
SEC23A	NM_006364	SEC23-related protein A
SLC11A2	NM_000617	solute carrier family 11 (proton-coupled
SLC30A9	NM_006345	solute carrier family 30 (zinc transporter),
SLC35A3	NM_012243	solute carrier family 35
SORBS3	NM_001018003	vinexin beta (SH3-containing adaptor molecule-1)
STS	NM_000351	steryl-sulfatase precursor
SYT1	NM_005639	synaptotagmin I
TBC1D2	NM_018421	TBC1 domain family, member 2
TFRC	NM_003234	transferrin receptor
TGFBR3	NM_003243	Transforming growth factor, beta receptor III
TPI1	NM_000365	triosephosphate isomerase 1
TXLNA	NM_175852	Taxilin
UBE2V2	NM_003350	ubiquitin-conjugating enzyme E2 variant 2
USP46	NM_022832	ubiquitin specific protease 46

VDAC1	NM_003374	voltage-dependent anion channel 1
VIL2	NM_003379	villin 2
WBSCR22	NM_017528	Williams Beuren syndrome chromosome region 22
WDR7	NM_015285	Rabconnectin-3 beta isoform 1
WNT7B	NM_058238	wingless-type MMTV integration site family,
YIPF3	NM_015388	natural killer cell-specific antigen KLIP1

Table 4A. Tumor associated mRNAs altered by hsa-miR-15 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
AKAP12	Akap12/SSeCKS/Gravin	Signal transduction	CRC, PC, LC, GC, AML, CML	(Xia *et al.*, 2001b; Wikman *et al.*, 2002; Boultwood *et al.*, 2004; Choi *et al.*, 2004; Mori *et al.*, 2006)
CCND3	cyclin D3	cell cycle	EC, TC, BldC, CRC, LSCC, BCL, PaC, M	(Florenes *et al.*, 2000; Ito *et al.*, 2001; Filipits *et al.*, 2002; Bai *et al.*, 2003; Pruneri *et al.*, 2005; Tanami *et al.*, 2005; Lopez-Beltran *et al.*, 2006; Troncone *et al.*, 2006; Wu *et al.*, 2006b)
CCNG2	cyclin G2	cell cycle	TC, SCCHN	(Alevizos *et al.*, 2001; Ito *et al.*, 2003b)
CDKN2C	CDK inhibitor 2C	cell cycle	HB, MB, HCC, HL, MM	(Iolascon *et al.*, 1998; Kulkarni *et al.*, 2002; Morishita *et al.*, 2004; Sanchez-Aguilera *et al.*, 2004)
CHUK	IKK alpha	Signal transduction	LSCC, BC	(Cao *et al.*, 2001; Nakayama *et al.*, 2001; Romieu-Mourez *et al.*, 2001)
CTGF	CTGF/ IGFBP-8	cell adhesion, migration	BC, GB, OepC, RMS, CRC, PC	(Hishikawa *et al.*, 1999; Shimo *et al.*, 2001; Koliopanos *et al.*, 2002; Pan *et al.*, 2002; Croci *et al.*, 2004; Lin *et al.*, 2005; Yang *et al.*, 2005)
EPAS1	EPAS-1	transcription	RCC, BldC, HCC	(Xia *et al.*, 2001a; Xia *et al.*, 2002; Bangoura *et al.*, 2004)
FGF2	FGF-2	Signal transduction	BC, RCC, OC, M, NSCLC	(Chandler *et al.*, 1999)
HSPA1B	HSP-70-1	protein chaperone	HCC, CRC, BC	(Ciocca *et al.*, 1993; Lazaris *et al.*, 1995; Lazaris *et al.*, 1997; Takashima *et al.*, 2003)
IGFBP3	IGFBP-3	Signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	Signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
LCN2	lipocalin 2/NGAL	cell adhesion	PaC, CRC, HCC, BC, OC	(Bartsch and Tschesche, 1995; Furutani *et al.*, 1998; Fernandez *et al.*, 2005; Lee *et al.*, 2006)
NF1	NF-1	Signal transduction	G, AC, NF, PCC, ML	(Rubin and Gutmann, 2005)
RBL1	p107	cell cycle	BCL, PC, CRC, TC	(Takimoto *et al.*, 1998; Claudio *et al.*, 2002; Wu *et al.*, 2002; Ito *et al.*, 2003a)
TACC1	TACC1	cell cycle	BC, OC	(Cully *et al.*, 2005; Lauffart *et al.*, 2005)
TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
VAV3	Vav3	Signal transduction	PC	(Dong *et al.*, 2006)
WISP2	WISP-2	Signal transduction	CRC, BC	(Pennica *et al.*, 1998; Saxena *et al.*, 2001)

WISP3	cyclin D1	cell cycle	MCL, BC, SCCHN, OepC, HCC, CRC, BldC, EC, OC, M, AC, GB, GC, PaC	(Donnellan and Chetty, 1998)
WISP4	eIF-4e	translation	BC, CRC, NHL, NB, CHN, LXC, BldC, PC, GC	(Graff and Zimmer, 2003)
WISP5	FGF-R4	Signal transduction	TC, BC, OC, PaC	(Jaakkola *et al.*, 1993; Shah *et al.*, 2002; Ezzat *et al.*, 2005)
WISP6	SKP-2	proteasomal degradation	PaC, OC, BC, MFS, GB, EC, NSCLC, PC	(Kamata *et al.*, 2005; Saigusa *et al.*, 2005; Shibahara *et al.*, 2005; Takanami, 2005; Einama *et al.*, 2006; Huang *et al.*, 2006; Sui *et al.*, 2006; Traub *et al.*, 2006)
WNT7B	Wnt-7b	Signal transduction	BC, BldC	(Huguet *et al.*, 1994; Bui *et al.*, 1998)

Abbreviations: AC, astrocytoma; AML, acute myeloid leukemia; BC, breast carcinoma; BCL, B-cell lymphoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CHN, carcinoma of the head and neck; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; EC, endometrial carcinoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HB, hepatoblastoma; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; LC, lung carcinoma; LSCC, laryngeal squamous cell carcinoma; LXC, larynx carcinoma; M, melanoma; MB, medulloblastoma; MCL, mantle cell lymphoma; MFS, myxofibrosarcoma; ML, myeloid leukemia; MM, multiple myeloma; NB, neuroblastoma; NF, neurofibroma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; PCC, pheochromocytoma; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SCCHN, squamous cell carcinoma of the head and neck; TC, thyroid carcinoma

Table 4B. Tumor associated mRNAs altered by hsa-miR-26 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
CTGF	CTGF/IGFBP-8	cell adhesion, migration	BC, GB, OepC, RMS, CRC, PC	(Hishikawa *et al.*, 1999; Shimo *et al.*, 2001; Koliopanos *et al.*, 2002; Pan *et al.*, 2002; Croci *et al.*, 2004; Lin *et al.*, 2005; Yang *et al.*, 2005)
EIF4E	eIF-4e	translation	BC, CRC, NHL, NB, CHN, LXC, BldC, PC, GC	(Graff and Zimmer, 2003)
EPHA2	EPH receptor A2	cell adhesion	M, NSCLC, BC, PC, CRC, OC	(Walker-Daniels *et al.*, 2003; Ireton and Chen, 2005; Landen *et al.*, 2005)
FAS	Fas	apoptosis	NSCLC, G, L, CRC, OepC	(Moller *et al.*, 1994; Gratas *et al.*, 1998; Martinez-Lorenzo *et al.*, 1998; Shinoura *et al.*, 2000; Viard-Leveugle *et al.*, 2003)
FZD7	Frizzled-7	signal transduction	OepC, GC, HCC	(Tanaka *et al.*, 1998; Kirikoshi *et al.*, 2001; Merle *et al.*, 2004)
GRB10	GRB10	signal	CeC	(Okino *et al.*, 2005)

		transduction		
IGFBP1	IGFBP-1	signal transduction	BC, CRC	(Firth and Baxter, 2002)
IGFBP3	IGFBP-3	signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
MCAM	MCAM	cell adhesion	M, AS, KS, LMS	(McGary *et al.*, 2002)
MCL1	Mcl-1	apoptosis	HCC, MM, TT, CL, ALCL, BCL, PC	(Krajewska *et al.*, 1996; Kitada *et al.*, 1998; Cho-Vega *et al.*, 2004; Rust *et al.*, 2005; Sano *et al.*, 2005; Wuilleme-Toumi *et al.*, 2005; Fleischer *et al.*, 2006; Sieghart *et al.*, 2006)
MVP	major vault protein	multi drug resistance	AML, CML, ALL, OC, BC, M, OS, NB, NSCLC	(Mossink *et al.*, 2003)
MYBL1	A-Myb	transcription	BL	(Golay *et al.*, 1996)
NRG1	Neuregulin 1	signal transduction	BC, PaC, G	(Adelaide *et al.*, 2003; Ritch *et al.*, 2003; Prentice *et al.*, 2005)
PBX1	PBX-1	transcription	ALL	(Aspland *et al.*, 2001)
PDCD4	Pdcd-4	apoptosis	G, HCC, L, RCC	(Chen *et al.*, 2003; Jansen *et al.*, 2004; Zhang *et al.*, 2006; Gao *et al.*, 2007)
PDGFRL	PDGFR-like	signal transduction	CRC, NSCLC, HCC, PC	(Fujiwara *et al.*, 1995; Komiya *et al.*, 1997)
PXN	Paxillin	cell adhesion, motility	SCLC, M	(Salgia *et al.*, 1999; Hamamura *et al.*, 2005)
RARRES1	RAR responder 1	migration, invasion	CRC, PC	(Zhang *et al.*, 2004; Wu *et al.*, 2006a)
TGFBR3	TGF beta receptor III	signal transduction	CeC, high grade NHL, CRC, BC	(Venkatasubbarao *et al.*, 2000; Bandyopadhyay *et al.*, 2002; Woszczyk *et al.*, 2004; Zhang *et al.*, 2004; Soufla *et al.*, 2005; Wu *et al.*, 2006a)
TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
VAV3	Vav3	signal transduction	PC	(Dong *et al.*, 2006)

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AS, angiosarcoma; BC, breast carcinoma; BCL, B-cell lymphoma; BL, Burkitt's lymphoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CHN, carcinoma of the head and neck; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HCC, hepatocellular carcinoma; KS, Kaposi's sarcoma; L, leukemia; LC, lung carcinoma; LMS, leiomyosarcoma; LXC, larynx carcinoma; M, melanoma; MM, multiple myeloma; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal

carcinoma; OS, osteosarcoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SCLC, small cell lung cancer; TT, testicular tumor.

Table 4C. Tumor associated mRNAs altered by hsa-miR-147 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
BCL6	BCL-6	apoptosis	NHL	(Carbone *et al.*, 1998; Butler *et al.*, 2002)
CCND1	cyclin D1	cell cycle	MCL, BC, SCCHN, OepC, HCC, CRC, BldC, EC, OC, M, AC, GB, GC, PaC	(Donnellan and Chetty, 1998)
CCNG1	cyclin G1	cell cycle	OS, BC, PC	(Skotzko *et al.*, 1995; Reimer *et al.*, 1999)
EPHB2	EPH receptor B2	signal transduction	PC, GC, CRC, OC, G, BC	(Huusko *et al.*, 2004; Nakada *et al.*, 2004; Wu *et al.*, 2004; Jubb *et al.*, 2005; Guo *et al.*, 2006; Kokko *et al.*, 2006; Wu *et al.*, 2006c; Davalos *et al.*, 2007)
EREG	epiregulin	signal transduction	BldC, CRC, PaC, PC	(Baba *et al.*, 2000; Torring *et al.*, 2000; Zhu *et al.*, 2000; Thogersen *et al.*, 2001)
ETS2	ETS-2	transcription	CeC, PC, TC, CRC, ESCC	(Simpson *et al.*, 1997; Sementchenko *et al.*, 1998; de Nigris *et al.*, 2001; Ito *et al.*, 2002; Li *et al.*, 2003)
FGFR3	FGF-R3	signal transduction	BldC, CRC, CeC, MM	(L'Hote and Knowles, 2005)
FGFR4	FGF receptor-4	signal transduction	TC, BC, OC, PaC	(Jaakkola *et al.*, 1993; Shah *et al.*, 2002; Ezzat *et al.*, 2005)
FZD7	Frizzled-7	signal transduction	OepC, GC, HCC	(Tanaka *et al.*, 1998; Kirikoshi *et al.*, 2001; Merle *et al.*, 2004)
ID4	inhibitor of DNA binding 4	transcription	BC, GC, L	(Chan *et al.*, 2003; Yu *et al.*, 2005; de Candia *et al.*, 2006)
IGFBP1	IGFBP-1	signal transduction	BC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
JAK1	Janus kinase 1	signal transduction	PC	(Rossi *et al.*, 2005)
JUN	c-Jun	transcription	HL, HCC	(Eferl *et al.*, 2003; Weiss and Bohmann, 2004)
LHFP	lipoma HMGIC fusion partner	transcription	Li	(Petit *et al.*, 1999)
LIMK1	LIM kinase 1	cell motility,	BC, PC	(Yoshioka *et al.*, 2003)

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		invasion		
P8	P8	transcription	BC, TC, PaC	(Ree *et al.*, 1999; Su *et al.*, 2001; Ito *et al.*, 2005)
PDCD4	Pdcd-4	apoptosis	G, HCC, L, RCC	(Chen *et al.*, 2003; Jansen *et al.*, 2004; Zhang *et al.*, 2006; Gao *et al.*, 2007)
RARRES1	RAR responder 1	migration, invasion	CRC, PC	(Zhang *et al.*, 2004; Wu *et al.*, 2006a)
RHOC	RhoC	cell motility, invasion	SCCHN, OepC, CRC, M, PC	(Bellovin *et al.*, 2006; Faried *et al.*, 2006; Kleer *et al.*, 2006; Ruth *et al.*, 2006; Yao *et al.*, 2006)
SKP2	SKP-2	proteasomal degradation	PaC, OC, BC, MFS, GB, EC, NSCLC, PC	(Kamata *et al.*, 2005; Saigusa *et al.*, 2005; Shibahara *et al.*, 2005; Takanami, 2005; Einama *et al.*, 2006; Huang *et al.*, 2006; Sui *et al.*, 2006; Traub *et al.*, 2006)
TGFBR2	TGF beta receptor type II	signal transduction	BC, CRC	(Markowitz, 2000; Lucke *et al.*, 2001; Biswas *et al.*, 2004)
VTN	vitronectin	cell adhesion	CRC, G, OC, M, BC	(Tomasini-Johansson *et al.*, 1994; Carreiras *et al.*, 1996; Lee *et al.*, 1998; Carreiras *et al.*, 1999; Uhm *et al.*, 1999; Aaboe *et al.*, 2003)

Abbreviations: AC, astrocytoma; BC, breast carcinoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CRC, colorectal carcinoma; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; L, leukemia; Li, lipoma; M, melanoma; MCL, mantle cell lymphoma; MFS, myxofibrosarcoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; OS, osteosarcoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TC, thyroid carcinoma

Table 4D. Tumor associated mRNAs altered by hsa-miR-188 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
AR	Androgen receptor	transcription	PC	(Feldman and Feldman, 2001)
BCL6	BCL-6	apoptosis	NHL	(Carbone *et al.*, 1998; Butler *et al.*, 2002)
ETS2	ETS-2	transcription	CeC, PC, TC, CRC, ESCC	(Simpson *et al.*, 1997; Sementchenko *et al.*, 1998; de Nigris *et al.*, 2001; Ito *et al.*, 2002; Li *et al.*, 2003)
FGF2	FGF-2	signal transduction	BC, RCC, OC, M, NSCLC	(Chandler *et al.*, 1999)
PTEN	PTEN	signal transduction	GB, OC, BC, EC, HCC, M, LC, TC, NHL, PC, BldC, CRC	(Guanti *et al.*, 2000; Shin *et al.*, 2001; Simpson and Parsons, 2001; Vivanco and Sawyers, 2002)
ST13	suppression of tumorigenicity 13	signal transduction	CRC	(Wang *et al.*, 2005)
TP73L	p63	transcription	CeC, PC, SCCHN, LC, BldC, BC, GC	(Moll and Slade, 2004)

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TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
VAV3	Vav3	signal transduction	PC	(Dong *et al.*, 2006)
WISP2	WISP-2	signal transduction	CRC, BC	(Pennica *et al.*, 1998; Saxena *et al.*, 2001)`
AREG	amphiregulin	signal transduction	HCC, NSCLC, MM, PC, OC, CRC, PaC, GC	(Kitadai *et al.*, 1993; Ebert *et al.*, 1994; Solic and Davies, 1997; D'Antonio *et al.*, 2002; Bostwick *et al.*, 2004; Ishikawa *et al.*, 2005; Mahtouk *et al.*, 2005; Castillo *et al.*, 2006)
CCNA2	cyclin A2	cell cycle	AML	(Qian *et al.*, 2002)
FAS	Fas	apoptosis	NSCLC, G, L, CRC, OepC	(Moller *et al.*, 1994; Gratas *et al.*, 1998; Martinez-Lorenzo *et al.*, 1998; Shinoura *et al.*, 2000; Viard-Leveugle *et al.*, 2003)
FGFBP1	FGF-BP	signal transduction	SCCHN, BC, CRC, PC, PaC	(Abuharbeid *et al.*, 2006; Tassi *et al.*, 2006)
HDAC3	HDAC-3	transcription	CRC, AC	(Liby *et al.*, 2006; Wilson *et al.*, 2006)
IGFBP3	IGFBP-3	signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
MCL1	Mcl-1	apoptosis	HCC, MM, TT, CL, ALCL, BCL, PC	(Krajewska *et al.*, 1996; Kitada *et al.*, 1998; Cho-Vega *et al.*, 2004; Rust *et al.*, 2005; Sano *et al.*, 2005; Wuilleme-Toumi *et al.*, 2005; Fleischer *et al.*, 2006; Sieghart *et al.*, 2006)
MYBL1	A-Myb	transcription	BL	(Golay *et al.*, 1996)
PRKCA	PKC alpha	signal transduction	BldC, PC, EC, BC, CRC, HCC, M, GC, OC	(Weichert *et al.*, 2003; Jiang *et al.*, 2004; Lahn and Sundell, 2004; Koivunen *et al.*, 2006)
RBL1	p107	cell cycle	BCL, PC, CRC, TC	(Takimoto *et al.*, 1998; Claudio *et al.*, 2002; Wu *et al.*, 2002; Ito *et al.*, 2003a)
ST7	suppressor of tumorigenicity 7	unknown	PC, BC	(Hooi *et al.*, 2006)
TGFBR3	TGF beta receptor III	signal transduction	CeC, high grade NHL, CRC, BC	(Venkatasubbarao *et al.*, 2000; Bandyopadhyay *et al.*, 2002; Woszczyk *et al.*, 2004; Soufla *et al.*, 2005)

Abbreviations: AC, astrocytoma; ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; BC, breast carcinoma; BCL, B-cell lymphoma; BL, Burkitt's lymphoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CLL, chronic lymphoblastic leukemia; CRC, colorectal carcinoma; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HCC, hepatocellular carcinoma; L, leukemia; LC, lung carcinoma; M, melanoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TC, thyroid carcinoma

Table 4E. Tumor associated mRNAs altered by hsa-miR-215 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
AKAP12	Akap12/SSeCKS/Gravin	signal transduction	CRC, PC, LC, GC, AML, CML	(Xia *et al.*, 2001b; Wikman *et al.*, 2002; Boultwood *et al.*, 2004; Choi *et al.*, 2004; Mori *et al.*, 2006)
ANG	angiogenin	angiogenesis	BC, OC, M, PaC, UC, CeC	(Barton *et al.*, 1997; Montero *et al.*, 1998; Hartmann *et al.*, 1999; Miyake *et al.*, 1999; Shimoyama *et al.*, 1999; Bodner-Adler *et al.*, 2001)
AREG	amphiregulin	signal transduction	HCC, NSCLC, MM, PC, OC, CRC, PaC, GC	(Kitadai *et al.*, 1993; Ebert *et al.*, 1994; Solic and Davies, 1997; D'Antonio *et al.*, 2002; Bostwick *et al.*, 2004; Ishikawa *et al.*, 2005; Mahtouk *et al.*, 2005; Castillo *et al.*, 2006)
BCL10	BCL-10	signal transduction	MALT BCL	(Thome, 2004)
BUB1	BUB1	chromosomal stability	AML, SGT, ALL, HL, L, CRC, GC	(Cahill *et al.*, 1998; Qian *et al.*, 2002; Ru *et al.*, 2002; Grabsch *et al.*, 2003; Shigeishi *et al.*, 2006)
CCND1	cyclin D1	cell cycle	MCL, BC, SCCHN, OepC, HCC, CRC, BldC, EC, OC, M, AC, GB, GC, PaC	(Donnellan and Chetty, 1998)
CCNG1	cyclin G1	cell cycle	OS, BC, PC	(Skotzko *et al.*, 1995; Reimer *et al.*, 1999)
CCNG2	cyclin G2	cell cycle	TC, SCCHN	(Alevizos *et al.*, 2001; Ito *et al.*, 2003b)
CTGF	CTGF/IGFBP-8	cell adhesion, migration	BC, GB, OepC, RMS, CRC, PC	(Hishikawa *et al.*, 1999; Shimo *et al.*, 2001; Koliopanos *et al.*, 2002; Pan *et al.*, 2002; Croci *et al.*, 2004; Lin *et al.*, 2005; Yang *et al.*, 2005)
EGFR	EGFR	signal transduction	SCCHN, G, BC, LC, OC, NSCLC	(Hynes and Lane, 2005)
EIF3S3	eIF-3 subunit 3g	translation	BC, PC, HCC	(Nupponen *et al.*, 1999; Nupponen *et al.*, 2000; Okamoto *et al.*, 2003)
EPAS1	EPAS-1	transcription	RCC, BldC, HCC	(Xia *et al.*, 2001a; Xia *et al.*, 2002; Bangoura *et al.*, 2004)
EPHA2	EPH receptor A2	cell adhesion	M, NSCLC, BC, PC, CRC, OC	(Walker-Daniels *et al.*, 2003; Ireton and Chen, 2005; Landen *et al.*, 2005)
EREG	epiregulin	signal transduction	BldC, CRC, PaC, PC	(Baba *et al.*, 2000; Torring *et al.*, 2000; Zhu *et al.*, 2000; Thogersen *et al.*, 2001)
ETS2	ETS-2	transcription	CeC, PC, TC, CRC, ESCC	(Simpson *et al.*, 1997; Sementchenko *et al.*, 1998; de Nigris *et al.*, 2001; Ito *et al.*, 2002; Li *et al.*, 2003)
FAS	Fas	apoptosis	NSCLC, G, L, CRC, OepC	(Moller *et al.*, 1994; Gratas *et al.*, 1998; Martinez-Lorenzo *et al.*, 1998; Shinoura *et al.*, 2000; Viard-Leveugle *et al.*, 2003)
FGF2	FGF-2	signal transduction	BC, RCC, OC, M, NSCLC	(Chandler *et al.*, 1999)

FGFBP1	FGF-BP	signal transduction	SCCHN, BC, CRC, PC, PaC	(Abuharbeid *et al.*, 2006; Tassi *et al.*, 2006)
FGFR1	FGF receptor-1	signal transduction	L, CRC, BC, RCC, OC, M, NSCLC	(Chandler *et al.*, 1999)
FGFR4	FGF receptor-4	signal transduction	TC, BC, OC, PaC	(Jaakkola *et al.*, 1993; Shah *et al.*, 2002; Ezzat *et al.*, 2005)
GRB10	GRB10	signal transduction	CeC	(Okino *et al.*, 2005)
IGFBP1	IGFBP-1	signal transduction	BC, CRC	(Firth and Baxter, 2002)
IGFBP3	IGFBP-3	signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
ILK	integrin-linked kinase	signal transduction	PC, CRC, GC, EWS, M, BC	(Hannigan *et al.*, 2005)
JUN	c-Jun	transcription	HL, HCC	(Eferl *et al.*, 2003; Weiss and Bohmann, 2004)
LCN2	lipocalin 2 / NGAL	cell adhesion	PaC, CRC, HCC, BC, OC	(Bartsch and Tschesche, 1995; Furutani *et al.*, 1998; Fernandez *et al.*, 2005; Lee *et al.*, 2006)
LIMK1	LIM kinase 1	cell motility, invasion	BC, PC	(Yoshioka *et al.*, 2003)
MCAM	MCAM	cell adhesion	M, AS, KS, LMS	(McGary *et al.*, 2002)
MCL1	Mcl-1	apoptosis	HCC, MM, TT, CL, ALCL, BCL, PC	(Krajewska *et al.*, 1996; Kitada *et al.*, 1998; Cho-Vega *et al.*, 2004; Rust *et al.*, 2005; Sano *et al.*, 2005; Wuilleme-Toumi *et al.*, 2005; Fleischer *et al.*, 2006; Sieghart *et al.*, 2006)
MDM2	Mdm2	proteasomal degradation	AC, GB, BC, CeC, OepC, L, HB, NSCLC, NPC, NB, OS, OC, EWS, Li, LS, Schw, TT, UC, WT, RMS	(Momand *et al.*, 1998)
MLF1	myeloid leukemia factor 1	cell cycle	AML	(Matsumoto *et al.*, 2000)
MVP	major vault protein	multi drug resistance	AML, CML, ALL, OC, BC, M, OS, NB, NSCLC	(Mossink *et al.*, 2003)
NF1	NF-1	signal transduction	G, AC, NF, PCC, ML	(Rubin and Gutmann, 2005)
NRG1	neuregulin 1	signal transduction	BC, PaC, G	(Adelaide *et al.*, 2003; Ritch *et al.*, 2003; Prentice *et al.*, 2005)

PBX1	PBX-1	transcription	ALL	(Aspland *et al.*, 2001)
PDCD4	Pdcd-4	apoptosis	G, HCC, L, RCC	(Chen *et al.*, 2003; Jansen *et al.*, 2004; Zhang *et al.*, 2006; Gao *et al.*, 2007)
PIK3CD	PI 3-kinase IA delta (p110 delta)	signal transduction	AML, MSS, GI	(Vogt *et al.*, 2006)
PLCB1	PLC-beta1	signal transduction	AML	(Lo Vasco *et al.*, 2004)
PTEN	PTEN	signal transduction	GB, OC, BC, EC, HCC, M, LC, TC, NHL, PC, BldC, CRC	(Guanti *et al.*, 2000; Shin *et al.*, 2001; Simpson and Parsons, 2001; Vivanco and Sawyers, 2002)
RARRES1	RAR responder 1	migration, invasion	CRC, PC	(Zhang *et al.*, 2004; Wu *et al.*, 2006a)
RASSF2	RASSF2	signal transduction	GC,CRC, OC	(Akino *et al.*, 2005; Endoh *et al.*, 2005; Lambros *et al.*, 2005)
RB1	Rb	cell cycle	RB, SCLC, NSCLC	(Sherr and McCormick, 2002; Dyer and Bremner, 2005)
RHOC	RhoC	cell motility, invasion	SCCHN, OepC, CRC, M, PC	(Bellovin *et al.*, 2006; Faried *et al.*, 2006; Kleer *et al.*, 2006; Ruth *et al.*, 2006; Yao *et al.*, 2006)
SFRP4	secreted frizzled-related protein 4	signal transduction	MT, CLL, SCCHN	(Lee *et al.*, 2004; Liu *et al.*, 2006; Marsit *et al.*, 2006)
SKP2	SKP-2	proteasomal degradation	PaC, OC, BC, MFS, GB, EC, NSCLC, PC	(Kamata *et al.*, 2005; Saigusa *et al.*, 2005; Shibahara *et al.*, 2005; Takanami, 2005; Einama *et al.*, 2006; Huang *et al.*, 2006; Sui *et al.*, 2006; Traub *et al.*, 2006)
SMAD3	SMAD-3	signal transduction	GC, CRC, HCC, BC, ALL	(Zhu *et al.*, 1998; Han *et al.*, 2004; Liu and Matsuura, 2005; Yamagata *et al.*, 2005; Yang *et al.*, 2006)
SRI	Sorcin	multi drug resistance	OC, BC, AML	(Parekh *et al.*, 2002; Tan *et al.*, 2003)
ST7	suppressor of tumorigenicity 7	unknown	PC, BC	(Hooi *et al.*, 2006)
TGFBR2	TGF beta receptor type II	signal transduction	BC, CRC	(Markowitz, 2000; Lucke *et al.*, 2001; Biswas *et al.*, 2004)
TGFBR3	TGF beta receptor III	signal transduction	CeC, high grade NHL, CRC, BC	(Venkatasubbarao *et al.*, 2000; Bandyopadhyay *et al.*, 2002; Woszczyk *et al.*, 2004; Soufla *et al.*, 2005)
TNFRSF10B	TRAIL-R2	apoptosis	NSCLC, SCCHN, GC, BC, NHL	(Adams *et al.*, 2005)
TPD52	tumor protein D52	signal transduction	BC, LC, PC, OC, EC, HCC	(Boutros *et al.*, 2004)
TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
VTN	vitronectin	cell adhesion	CRC, G, OC, M, BC	(Tomasini-Johansson *et al.*, 1994; Carreiras *et al.*, 1996; Lee *et al.*,

				1998; Carreiras *et al.*, 1999; Uhm *et al.*, 1999; Aaboe *et al.*, 2003)
WISP2	WISP-2	signal transduction	CRC, BC	(Pennica *et al.*, 1998; Saxena *et al.*, 2001)`

Abbreviations: AC, astrocytoma; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AS, angiosarcoma; BC, breast carcinoma; BCL, B-cell lymphoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; EWS, Ewing's sarcoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; GI, gastrinoma; HB, hepatoblastoma; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; KS, Kaposi's sarcoma; L, leukemia; LC, lung carcinoma; Li, lipoma; LMS, leiomyosarcoma; LS, liposarcoma; M, melanoma; MALT BCL, mucosa-associated lymphoid tissue B-cell lymphoma; MCL, mantle cell lymphoma; MFS, myxofibrosarcoma; ML, myeloid leukemia; MM, multiple myeloma; MSS, high-risk myelodysplastic syndrome; MT, mesothelioma; NB, neuroblastoma; NF, neurofibroma; NHL, non-Hodgkin lymphoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; OS, osteosarcoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; PCC, pheochromocytoma; RB, retinoblastoma; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SCCHN, squamous cell carcinoma of the head and neck; Schw, schwannoma; SCLC, small cell lung cancer; SGT, salivary gland tumor; TC, thyroid carcinoma; TT, testicular tumor; UC, urothelial carcinoma; WT, Wilm's tumor

Table 4F. Tumor associated mRNAs altered by hsa-miR-216 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
BCL10	BCL-10	signal transduction	MALT BCL	(Thome, 2004)
BRCA1	BRCA-1	chromosomal stability	BC, OC	(Wooster and Weber, 2003)
CCNG1	cyclin G1	cell cycle	OS, BC, PC	(Skotzko *et al.*, 1995; Reimer *et al.*, 1999)
CDK4	CDK-4	cell cycle	G, GB, BC, LC, GC, EC, L, OS, OC, TT, HCC, CHN	(Malumbres and Barbacid, 2001)
EGFR	EGFR	signal transduction	SCCHN, G, BC, LC, OC, NSCLC	(Hynes and Lane, 2005)
FAS	Fas	apoptosis	NSCLC, G, L, CRC, OepC	(Moller *et al.*, 1994; Gratas *et al.*, 1998; Martinez-Lorenzo *et al.*, 1998; Shinoura *et al.*, 2000; Viard-Leveugle *et al.*, 2003)
HDAC3	HDAC-3	transcription	CRC, AC	(Liby *et al.*, 2006; Wilson *et al.*, 2006)
JUN	c-Jun	transcription	HL, HCC	(Eferl *et al.*, 2003; Weiss and Bohmann, 2004)
NF1	NF-1	signal transduction	G, AC, NF, PCC, ML	(Rubin and Gutmann, 2005)
RARRES1	RAR responder 1	migration, invasion	CRC, PC	(Zhang *et al.*, 2004; Wu *et al.*, 2006a)
ST7	suppressor of tumorigenicity 7	unknown	PC, BC	(Hooi *et al.*, 2006)

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TGFBR3	TGF beta receptor III	signal transduction	CeC, high grade NHL, CRC, BC	(Venkatasubbarao *et al.*, 2000; Bandyopadhyay *et al.*, 2002; Woszczyk *et al.*, 2004; Soufla *et al.*, 2005)
VAV3	Vav3	signal transduction	PC	(Dong *et al.*, 2006)
WISP2	WISP-2	signal transduction	CRC, BC	(Pennica *et al.*, 1998; Saxena *et al.*, 2001)`

Abbreviations: AC, astrocytoma; BC, breast carcinoma; CeC, cervical carcinoma; CHN, carcinoma of the head and neck; CRC, colorectal carcinoma; EC, endometrial carcinoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; L, leukemia; LC, lung carcinoma; MALT BCL, mucosa-associated lymphoid tissue B-cell lymphoma; ML, myeloid leukemia; NF, neurofibroma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; OS, osteosarcoma; PC, prostate carcinoma; PCC, pheochromocytoma; SCCHN, squamous cell carcinoma of the head and neck; TT, testicular tumor

Table 4G. Tumor associated mRNAs altered by hsa-miR-331 having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
AR	Androgen receptor	transcription	PC	(Feldman and Feldman, 2001)
AREG	amphiregulin	signal transduction	HCC, NSCLC, MM, PC, OC, CRC, PaC, GC	(Kitadai *et al.*, 1993; Ebert *et al.*, 1994; Solic and Davies, 1997; D'Antonio *et al.*, 2002; Bostwick *et al.*, 2004; Ishikawa *et al.*, 2005; Mahtouk *et al.*, 2005; Castillo *et al.*, 2006)
CCNG1	cyclin G1	cell cycle	OS, BC, PC	(Skotzko *et al.*, 1995; Reimer *et al.*, 1999)
EREG	epiregulin	signal transduction	BldC, CRC, PaC, PC	(Baba *et al.*, 2000; Torring *et al.*, 2000; Zhu *et al.*, 2000; Thogersen *et al.*, 2001)
FGFR1	FGF receptor-1	signal transduction	L, CRC, BC, RCC, OC, M, NSCLC	(Chandler *et al.*, 1999)
IGFBP3	IGFBP-3	signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
PDCD4	Pdcd-4	apoptosis	G, HCC, L, RCC	(Chen *et al.*, 2003; Jansen *et al.*, 2004; Zhang *et al.*, 2006; Gao *et al.*, 2007)
PDPK1	PDK-1	signal transduction	BC	(Zeng *et al.*, 2002; Tseng *et al.*, 2006; Xie *et al.*, 2006)
PHLPP	PHLPP	signal transduction	CRC, GB	(Matsumoto *et al.*, 2000)
PXN	paxillin	cell adhesion, motility	SCLC, M	(Salgia *et al.*, 1999; Hamamura *et al.*, 2005)
SKP2	SKP-2	proteasomal degradation	PaC, OC, BC, MFS, GB, EC, NSCLC, PC	(Kamata *et al.*, 2005; Saigusa *et al.*, 2005; Shibahara *et al.*, 2005; Takanami, 2005; Einama *et al.*, 2006; Huang *et al.*, 2006; Sui *et al.*,

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				2006; Traub *et al.*, 2006)
TGFB2	TGF beta-2	signal transduction	PaC, CRC, BC, M	(Krasagakis *et al.*, 1998; Jonson *et al.*, 2001; Nakagawa *et al.*, 2004; Beisner *et al.*, 2006)
TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
WNT7B	Wnt-7b	signal transduction	BC, BldC	(Huguet *et al.*, 1994; Bui *et al.*, 1998)

Abbreviations: BC, breast carcinoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CRC, colorectal carcinoma; EC, endometrial carcinoma; G, glioma; GB, glioblastoma; HCC, hepatocellular carcinoma; L, leukemia; LC, lung carcinoma; M, melanoma; MFS, myxofibrosarcoma; MM, multiple myeloma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OS, osteosarcoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

Table 4H. Tumor associated mRNAs altered by mmu-miR-292-3p having prognostic or therapeutic value for the treatment of various malignancies.

Gene Symbol	Gene Title	Cellular Process	Cancer Type	Reference
AR	Androgen receptor	transcription	PC	(Feldman and Feldman, 2001)
CCND3	cyclin D3	cell cycle	EC, TC, BldC, CRC, LSCC, BCL, PaC, M	(Florenes *et al.*, 2000; Ito *et al.*, 2001; Filipits *et al.*, 2002; Bai *et al.*, 2003; Pruneri *et al.*, 2005; Tanami *et al.*, 2005; Lopez-Beltran *et al.*, 2006; Troncone *et al.*, 2006; Wu *et al.*, 2006b)
CCNG1	cyclin G1	cell cycle	OS, BC, PC	(Skotzko *et al.*, 1995; Reimer *et al.*, 1999)
CEBPD	C/EBP delta	transcription	PC	(Yang *et al.*, 2001)
CSF1	CSF-1	signal transduction	HCC, LC	(Budhu *et al.*, 2006; Uemura *et al.*, 2006)
FAS	Fas	apoptosis	NSCLC, G, L, CRC, OepC	(Moller *et al.*, 1994; Gratas *et al.*, 1998; Martinez-Lorenzo *et al.*, 1998; Shinoura *et al.*, 2000; Viard-Leveugle *et al.*, 2003)
FGFBP1	FGF-BP	signal transduction	SCCHN, BC, CRC, PC, PaC	(Abuharbeid *et al.*, 2006; Tassi *et al.*, 2006)
HSPCA	Hsp90 1alpha	invasion	FS	(Eustace *et al.*, 2004)
IGFBP3	IGFBP-3	signal transduction	BC, PC, LC, CRC	(Firth and Baxter, 2002)
IL8	IL-8	signal transduction	BC, CRC, PaC, NSCLC, PC, HCC	(Akiba *et al.*, 2001; Sparmann and Bar-Sagi, 2004)
LMO4	Lmo-4	transcription	BC, SCCHN, SCLC	(Visvader *et al.*, 2001; Mizunuma *et al.*, 2003; Taniwaki *et al.*, 2006)
MCAM	MCAM	cell adhesion	M, AS, KS, LMS	(McGary *et al.*, 2002)
MCL1	Mcl-1	apoptosis	HCC, MM, TT, CL, ALCL, BCL, PC	(Krajewska *et al.*, 1996; Kitada *et al.*, 1998; Cho-Vega *et al.*, 2004; Rust *et al.*, 2005; Sano *et al.*, 2005; Wuilleme-Toumi *et al.*, 2005; Fleischer *et*

				al., 2006; Sieghart *et al.*, 2006)
MDM2	Mdm2	proteasomal degradation	AC, GB, BC, CeC, OepC, L, HB, NSCLC, NPC, NB, OS, OC, EWS, Li, LS, Schw, TT, UC, WT, RMS	(Momand *et al.*, 1998)
MVP	major vault protein	multi drug resistance	AML, CML, ALL, OC, BC, M, OS, NB, NSCLC	(Mossink *et al.*, 2003)
PDCD4	Pdcd-4	apoptosis	G, HCC, L, RCC	(Chen *et al.*, 2003; Jansen *et al.*, 2004; Zhang *et al.*, 2006; Gao *et al.*, 2007)
PDGFRL	PDGFR-like	signal transduction	CRC, NSCLC, HCC, PC	(Fujiwara *et al.*, 1995; Komiya *et al.*, 1997)
PTEN	PTEN	signal transduction	GB, OC, BC, EC, HCC, M, LC, TC, NHL, PC, BldC, CRC	(Guanti *et al.*, 2000; Shin *et al.*, 2001; Simpson and Parsons, 2001; Vivanco and Sawyers, 2002)
SKP2	SKP-2	proteasomal degradation	PaC, OC, BC, MFS, GB, EC, NSCLC, PC	(Kamata *et al.*, 2005; Saigusa *et al.*, 2005; Shibahara *et al.*, 2005; Takanami, 2005; Einama *et al.*, 2006; Huang *et al.*, 2006; Sui *et al.*, 2006; Traub *et al.*, 2006)
TGFBR3	TGF beta receptor III	signal transduction	CeC, high grade NHL, CRC, BC	(Venkatasubbarao *et al.*, 2000; Bandyopadhyay *et al.*, 2002; Woszczyk *et al.*, 2004; Soufla *et al.*, 2005)
TNFRSF10B	TRAIL-R2	apoptosis	NSCLC, SCCHN, GC, BC, NHL	(Adams *et al.*, 2005)
TPD52L1	Tumor protein D52-like 1	cell cycle	BC	(Boutros and Byrne, 2005)
TXN	thioredoxin (trx)	thioredoxin redox system	LC, PaC, CeC, HCC	(Marks, 2006)
WNT7B	Wnt-7b	signal transduction	BC, BldC	(Huguet *et al.*, 1994; Bui *et al.*, 1998)

Abbreviations: AC, astrocytoma; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AS, angiosarcoma; BC, breast carcinoma; BCL, B-cell lymphoma; BldC, bladder carcinoma; CeC, cervical carcinoma; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; EC, endometrial carcinoma; EWS, Ewing's sarcoma; FS, fibrosarcoma; G, glioma; GB, glioblastoma; GC, gastric carcinoma; HB, hepatoblastoma; HCC, hepatocellular carcinoma; KS, Kaposi's sarcoma; L, leukemia; LC, lung carcinoma; Li, lipoma; LMS, leiomyosarcoma; LS, liposarcoma; LSCC, laryngeal squamous cell carcinoma; M, melanoma; MFS, myxofibrosarcoma; MM, multiple myeloma; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung carcinoma; OC, ovarian carcinoma; OepC, oesophageal carcinoma; OS, osteosarcoma; PaC, pancreatic carcinoma; PC, prostate carcinoma; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SCCHN, squamous cell carcinoma of the head and neck; Schw, schwannoma; SCLC, small cell lung cancer; TC, thyroid carcinoma; TT, testicular tumor; UC, urothelial carcinoma; WT, Wilm's tumor

The methods can further comprise one or more of the steps including: (a) obtaining a sample from the patient, (b) isolating nucleic acids from the sample, (c) labeling the nucleic acids isolated from the sample, and (d) hybridizing the labeled nucleic acids to one or more probes. Nucleic acids of the invention include one or more nucleic acid comprising at least one segment having a sequence or complementary sequence of to a nucleic acid representative of one or more of genes or markers in Table 1, 3, and/or 4.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein and that different embodiments may be combined. Certain embodiments of the invention include determining expression of one or more marker, gene, or nucleic acid representative thereof, by using an amplification assay, a hybridization assay, or protein assay, a variety of which are well known to one of ordinary skill in the art. In certain aspects, an amplification assay can be a quantitative amplification assay, such as quantitative RT-PCR or the like. In still further aspects, a hybridization assay can include array hybridization assays or solution hybridization assays. The nucleic acids from a sample may be labeled from the sample and/or hybridizing the labeled nucleic acid to one or more nucleic acid probes. Nucleic acids, mRNA, and/or nucleic acid probes may be coupled to a support. Such supports are well known to those of ordinary skill in the art and include, but are not limited to glass, plastic, metal, or latex. In particular aspects of the invention, the support can be planar or in the form of a bead or other geometric shapes or configurations known in the art. Protein is typically assayed by immunoblotting, chromatography, or mass spectrometry or other methods known to those of ordinary skill in the art.

The present invention also concerns kits containing compositions of the invention or compositions to implement methods of the invention. In some embodiments, kits can be used to evaluate one or more marker molecules, and/or express one or more miRNA. In certain embodiments, a kit contains, contains at least or contains at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 100, 150, 200 or more probes, recombinant nucleic acid, or synthetic nucleic acid molecules related to the markers to be assessed or an miRNA to be expressed or modulated, and may include any

range or combination derivable therein. Kits may comprise components, which may be individually packaged or placed in a container, such as a tube, bottle, vial, syringe, or other suitable container means. Individual components may also be provided in a kit in concentrated amounts; in some embodiments, a component is provided individually in the same concentration as it would be in a solution with other components. Concentrations of components may be provided as 1x, 2x, 5x, 10x, or 20x or more. Kits for using probes, synthetic nucleic acids, recombinant nucleic acids, or non-synthetic nucleic acids of the invention for therapeutic, prognostic, or diagnostic applications are included as part of the invention. Specifically contemplated are any such molecules corresponding to any miRNA reported to influence biological activity or expression of one or more marker gene or gene pathway described herein. In certain aspects, negative and/or positive controls are included in some kit embodiments. The control molecules can be used to verify transfection efficiency and/or control for transfection-induced changes in cells.

Certain embodiments are directed to a kit for assessment of a pathological condition or the risk of developing a pathological condition in a patient by nucleic acid profiling of a sample comprising, in suitable container means, two or more nucleic acid hybridization or amplification reagents. The kit can comprise reagents for labeling nucleic acids in a sample and/or nucleic acid hybridization reagents. The hybridization reagents typically comprise hybridization probes. Amplification reagents include, but are not limited to amplification primers, reagents, and enzymes.

In some embodiments of the invention, an expression profile is generated by steps that include: (a) labeling nucleic acid in the sample; (b) hybridizing the nucleic acid to a number of probes, or amplifying a number of nucleic acids, and (c) determining and/or quantitating nucleic acid hybridization to the probes or detecting and quantitating amplification products, wherein an expression profile is generated. See U.S. Provisional Patent Application 60/575,743 and the U.S. Provisional Patent Application 60/649,584, and U.S. Patent Application Serial No. 11/141,707 and U.S. Patent Application Serial No. 11/273,640, all of which are hereby incorporated by reference.

Methods of the invention involve diagnosing and/or assessing the prognosis of a patient based on a miRNA and/or a marker nucleic acid expression profile. In certain embodiments, the elevation or reduction in the level of expression of a particular gene or genetic pathway or set of nucleic acids in a cell is correlated with a disease state or pathological condition compared to the expression level of the same in a normal or non-pathologic cell or tissue sample. This correlation allows for diagnostic and/or prognostic methods to be carried out when the expression level of one or more nucleic acid is measured in a biological sample being assessed and then compared to the expression level of a normal or non-pathologic cell or tissue sample. It is specifically contemplated that expression profiles for patients, particularly those suspected of having or having a propensity for a particular disease or condition such as cancer, can be generated by evaluating any of or sets of the miRNAs and/or nucleic acids discussed in this application. The expression profile that is generated from the patient will be one that provides information regarding the particular disease or condition. In many embodiments, the profile is generated using nucleic acid hybridization or amplification, (*e.g.*, array hybridization or RT-PCR). In certain aspects, an expression profile can be used in conjunction with other diagnostic and/or prognostic tests, such as histology, protein profiles in the serum and/or cytogenetic assessment.

The methods can further comprise one or more of the steps including: (a) obtaining a sample from the patient, (b) isolating nucleic acids from the sample, (c) labeling the nucleic acids isolated from the sample, and (d) hybridizing the labeled nucleic acids to one or more probes. Nucleic acids of the invention include one or more nucleic acid comprising at least one segment having a sequence or complementary sequence of to a nucleic acid representative of one or more of genes or markers in Table 1, 3, and/or 4.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein and that different embodiments may be combined. It is specifically contemplated that any methods and compositions discussed herein with respect to miRNA molecules, miRNA, genes and nucleic acids representative of genes may be implemented with respect to synthetic nucleic acids. In some embodiments the synthetic nucleic acid is exposed to the proper conditions to allow it to become a processed or mature nucleic acid, such as a miRNA under physiological

circumstances. The claims originally filed are contemplated to cover claims that are multiply dependent on any filed claim or combination of filed claims.

Also, any embodiment of the invention involving specific genes (including representative fragments there of), mRNA, or miRNAs by name is contemplated also to cover embodiments involving miRNAs whose sequences are at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% identical to the mature sequence of the specified miRNA.

It will be further understood that shorthand notations are employed such that a generic description of a gene or marker, or of a miRNA refers to any of its gene family members or representative fragments, unless otherwise indicated. It is understood by those of skill in the art that a "gene family" refers to a group of genes having similar coding sequence or miRNA coding sequence. Typically, miRNA members of a gene family are identified by a number following the initial designation. For example, miR-16-1 and miR-16-2 are members of the miR-16 gene family and "mir-7" refers to miR-7-1, miR-7-2 and miR-7-3. Moreover, unless otherwise indicated, a shorthand notation refers to related miRNAs (distinguished by a letter). Exceptions to these shorthand notations will be otherwise identified.

Other embodiments of the invention are discussed throughout this application. Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well and *vice versa*. The embodiments in the Example and Detailed Description section are understood to be embodiments of the invention that are applicable to all aspects of the invention.

The terms "inhibiting," "reducing," or "prevention," or any variation of these terms, when used in the claims and/or the specification includes any measurable decrease or complete inhibition to achieve a desired result.

The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1 illustrates percent proliferation of hsa-miR-147 treated cells relative to cells treated with negative control miRNA (= 100%). Standard deviations are indicated in the graphs.

FIG. 2 illustrates percent proliferation of hsa-miR-147 treated cells relative to cells treated with negative control miRNA (= 100%). Standard deviations are indicated in the graphs.

FIG. 3 shows that increasing amounts of negative control miRNA had no effect on cellular proliferation of A549 or H1299 cells. In contrast, the growth-inhibitory phenotype of hsa-miR-147 is dose-dependent and correlates with increasing amounts of hsa-miR-147. Hsa-miR-147 induces a therapeutic response at concentrations as low as 300 pM

FIG. 4 shows that the transfection of 300 pM hsa-miR-147 reduces proliferation of H460 cells by 23%. Maximal activity of singly administered miRNAs was observed with hsa-miR-124a, diminished cellular proliferation by 30.6%. Additive activity of pair-wise combinations (*e.g.*, hsa-miR-147 plus hsa-miR-124a) is defined as an activity that is greater than the sole activity of each miRNA.

FIG. 5 illustrates tumor volumes derived from NC-treated cells and hsa-miR-147-treated cells were averaged and plotted over time.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compositions and methods relating to the identification and characterization of genes and biological pathways related to these genes as represented by the expression of the identified genes, as well as use of miRNAs related to such, for therapeutic, prognostic, and diagnostic applications, particularly those methods and compositions related to assessing and/or identifying pathological conditions directly or indirectly related to miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p expression or the aberrant expression thereof.

In certain aspects, the invention is directed to methods for the assessment, analysis, and/or therapy of a cell or subject where certain genes have a reduced or increased expression (relative to normal) as a result of an increased or decreased expression of any one or a combination of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p family members (including, but not limited to SEQ ID NO:1 to SEQ ID NO:391) and/or genes with an increased expression (relative to normal) as a result of decreased expression thereof. The expression profile and/or response to miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p expression or inhibition may be indicative of a disease or pathological condition, *e.g.*, cancer.

Prognostic assays featuring any one or combination of the miRNAs listed or the markers listed (including nucleic acids representative thereof) could be used in assessment of a patient to determine what if any treatment regimen is justified. As with the diagnostic assays mentioned above, the absolute values that define low expression will depend on the platform used to

measure the miRNA(s). The same methods described for the diagnostic assays could be used for prognostic assays.

I. THERAPEUTIC METHODS

Embodiments of the invention concern nucleic acids that perform the activities of or inhibit endogenous miRNAs when introduced into cells. In certain aspects, nucleic acids are synthetic or non-synthetic miRNA. Sequence-specific miRNA inhibitors can be used to inhibit sequentially or in combination the activities of one or more endogenous miRNAs in cells, as well those genes and associated pathways modulated by the endogenous miRNA.

The present invention concerns, in some embodiments, short nucleic acid molecules that function as miRNAs or as inhibitors of miRNA in a cell. The term "short" refers to a length of a single polynucleotide that is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 50, 100, or 150 nucleotides or fewer, including all integers or ranges derivable there between. The nucleic acid molecules are typically synthetic. The term "synthetic" refers to a nucleic acid molecule that is not produced naturally in a cell. In certain aspects the chemical structure deviates from a naturally-occurring nucleic acid molecule, such as an endogenous precursor miRNA or miRNA molecule or complement thereof. While in some embodiments, nucleic acids of the invention do not have an entire sequence that is identical or complementary to a sequence of a naturally-occurring nucleic acid, such molecules may encompass all or part of a naturally-occurring sequence or a complement thereof. It is contemplated, however, that a synthetic nucleic acid administered to a cell may subsequently be modified or altered in the cell such that its structure or sequence is the same as non-synthetic or naturally occurring nucleic acid, such as a mature miRNA sequence. For example, a synthetic nucleic acid may have a sequence that differs from the sequence of a precursor miRNA, but that sequence may be altered once in a cell to be the same as an endogenous, processed miRNA or an inhibitor thereof. The term "isolated" means that the nucleic acid molecules of the invention are initially separated from different (in terms of sequence or structure) and unwanted nucleic acid molecules such that a population of isolated nucleic acids is at least about 90% homogenous, and may be at least about 95, 96, 97, 98, 99, or 100% homogenous with respect to other polynucleotide molecules. In many embodiments of the invention, a nucleic acid is isolated by virtue of it having been synthesized *in vitro* separate from endogenous nucleic acids in a cell. It will be understood, however, that isolated nucleic acids

may be subsequently mixed or pooled together. In certain aspects, synthetic miRNA of the invention are RNA or RNA analogs. miRNA inhibitors may be DNA or RNA, or analogs thereof. miRNA and miRNA inhibitors of the invention are collectively referred to as "synthetic nucleic acids."

In some embodiments, there is a miRNA or a synthetic miRNA having a length of between 17 and 130 residues. The present invention concerns miRNA or synthetic miRNA molecules that are, are at least, or are at most 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 140, 145, 150, 160, 170, 180, 190, 200 or more residues in length, including any integer or any range there between.

In certain embodiments, synthetic miRNA have (a) a "miRNA region" whose sequence or binding region from 5' to 3' is identical or complementary to all or a segment of a mature miRNA sequence, and (b) a "complementary region" whose sequence from 5' to 3' is between 60% and 100% complementary to the miRNA sequence in (a). In certain embodiments, these synthetic miRNA are also isolated, as defined above. The term "miRNA region" refers to a region on the synthetic miRNA that is at least 75, 80, 85, 90, 95, or 100% identical, including all integers there between, to the entire sequence of a mature, naturally occurring miRNA sequence or a complement thereof. In certain embodiments, the miRNA region is or is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% identical to the sequence of a naturally-occurring miRNA or complement thereof.

The term "complementary region" or "complement" refers to a region of a nucleic acid or mimetic that is or is at least 60% complementary to the mature, naturally occurring miRNA sequence. The complementary region is or is at least 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% complementary, or any range derivable therein. With single polynucleotide sequences, there may be a hairpin loop

structure as a result of chemical bonding between the miRNA region and the complementary region. In other embodiments, the complementary region is on a different nucleic acid molecule than the miRNA region, in which case the complementary region is on the complementary strand and the miRNA region is on the active strand.

In other embodiments of the invention, there are synthetic nucleic acids that are miRNA inhibitors. A miRNA inhibitor is between about 17 to 25 nucleotides in length and comprises a 5' to 3' sequence that is at least 90% complementary to the 5' to 3' sequence of a mature miRNA. In certain embodiments, a miRNA inhibitor molecule is 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length, or any range derivable therein. Moreover, an miRNA inhibitor may have a sequence (from 5' to 3') that is or is at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 or 100% complementary, or any range derivable therein, to the 5' to 3' sequence of a mature miRNA, particularly a mature, naturally occurring miRNA. One of skill in the art could use a portion of the miRNA sequence that is complementary to the sequence of a mature miRNA as the sequence for a miRNA inhibitor. Moreover, that portion of the nucleic acid sequence can be altered so that it is still comprises the appropriate percentage of complementarity to the sequence of a mature miRNA.

In some embodiments, of the invention, a synthetic miRNA or inhibitor contains one or more design element(s). These design elements include, but are not limited to: (i) a replacement group for the phosphate or hydroxyl of the nucleotide at the 5' terminus of the complementary region; (ii) one or more sugar modifications in the first or last 1 to 6 residues of the complementary region; or, (iii) noncomplementarity between one or more nucleotides in the last 1 to 5 residues at the 3' end of the complementary region and the corresponding nucleotides of the miRNA region. A variety of design modifications are known in the art, see below.

In certain embodiments, a synthetic miRNA has a nucleotide at its 5' end of the complementary region in which the phosphate and/or hydroxyl group has been replaced with another chemical group (referred to as the "replacement design"). In some cases, the phosphate group is replaced, while in others, the hydroxyl group has been replaced. In particular embodiments, the replacement group is biotin, an amine group, a lower alkylamine group, an acetyl group, 2'O-Me (2'oxygen-methyl), DMTO (4,4'-dimethoxytrityl with oxygen),

fluoroscein, a thiol, or acridine, though other replacement groups are well known to those of skill in the art and can be used as well. This design element can also be used with a miRNA inhibitor.

Additional embodiments concern a synthetic miRNA having one or more sugar modifications in the first or last 1 to 6 residues of the complementary region (referred to as the "sugar replacement design"). In certain cases, there is one or more sugar modifications in the first 1, 2, 3, 4, 5, 6 or more residues of the complementary region, or any range derivable therein. In additional cases, there are one or more sugar modifications in the last 1, 2, 3, 4, 5, 6 or more residues of the complementary region, or any range derivable therein, have a sugar modification. It will be understood that the terms "first" and "last" are with respect to the order of residues from the 5' end to the 3' end of the region. In particular embodiments, the sugar modification is a 2'O-Me modification. In further embodiments, there are one or more sugar modifications in the first or last 2 to 4 residues of the complementary region or the first or last 4 to 6 residues of the complementary region. This design element can also be used with a miRNA inhibitor. Thus, an miRNA inhibitor can have this design element and/or a replacement group on the nucleotide at the 5' terminus, as discussed above.

In other embodiments of the invention, there is a synthetic miRNA or inhibitor in which one or more nucleotides in the last 1 to 5 residues at the 3' end of the complementary region are not complementary to the corresponding nucleotides of the miRNA region ("noncomplementarity") (referred to as the "noncomplementarity design"). The noncomplementarity may be in the last 1, 2, 3, 4, and/or 5 residues of the complementary miRNA. In certain embodiments, there is noncomplementarity with at least 2 nucleotides in the complementary region.

It is contemplated that synthetic miRNA of the invention have one or more of the replacement, sugar modification, or noncomplementarity designs. In certain cases, synthetic RNA molecules have two of them, while in others these molecules have all three designs in place.

The miRNA region and the complementary region may be on the same or separate polynucleotides. In cases in which they are contained on or in the same polynucleotide, the miRNA molecule will be considered a single polynucleotide. In embodiments in which the

different regions are on separate polynucleotides, the synthetic miRNA will be considered to be comprised of two polynucleotides.

When the RNA molecule is a single polynucleotide, there can be a linker region between the miRNA region and the complementary region. In some embodiments, the single polynucleotide is capable of forming a hairpin loop structure as a result of bonding between the miRNA region and the complementary region. The linker constitutes the hairpin loop. It is contemplated that in some embodiments, the linker region is, is at least, or is at most 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 residues in length, or any range derivable therein. In certain embodiments, the linker is between 3 and 30 residues (inclusive) in length.

In addition to having a miRNA or inhibitor region and a complementary region, there may be flanking sequences as well at either the 5' or 3' end of the region. In some embodiments, there is or is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 nucleotides or more, or any range derivable therein, flanking one or both sides of these regions.

Methods of the invention include reducing or eliminating activity of one or more miRNAs in a cell comprising introducing into a cell a miRNA inhibitor (which may be described generally herein as an miRNA, so that a description of miRNA, where appropriate, also will refer to a miRNA inhibitor); or supplying or enhancing the activity of one or more miRNAs in a cell. The present invention also concerns inducing certain cellular characteristics by providing to a cell a particular nucleic acid, such as a specific synthetic miRNA molecule or a synthetic miRNA inhibitor molecule. However, in methods of the invention, the miRNA molecule or miRNA inhibitor need not be synthetic. They may have a sequence that is identical to a naturally occurring miRNA or they may not have any design modifications. In certain embodiments, the miRNA molecule and/or the miRNA inhibitor are synthetic, as discussed above.

The particular nucleic acid molecule provided to the cell is understood to correspond to a particular miRNA in the cell, and thus, the miRNA in the cell is referred to as the "corresponding miRNA." In situations in which a named miRNA molecule is introduced into a cell, the corresponding miRNA will be understood to be the induced or inhibited miRNA or induced or inhibited miRNA function. It is contemplated, however, that the miRNA molecule introduced

into a cell is not a mature miRNA but is capable of becoming or functioning as a mature miRNA under the appropriate physiological conditions. In cases in which a particular corresponding miRNA is being inhibited by a miRNA inhibitor, the particular miRNA will be referred to as the "targeted miRNA." It is contemplated that multiple corresponding miRNAs may be involved. In particular embodiments, more than one miRNA molecule is introduced into a cell. Moreover, in other embodiments, more than one miRNA inhibitor is introduced into a cell. Furthermore, a combination of miRNA molecule(s) and miRNA inhibitor(s) may be introduced into a cell. The inventors contemplate that a combination of miRNA may act at one or more points in cellular pathways of cells with aberrant phenotypes and that such combination may have increased efficacy on the target cell while not adversely effecting normal cells. Thus, a combination of miRNA may have a minimal adverse effect on a subject or patient while supplying a sufficient therapeutic effect, such as amelioration of a condition, growth inhibition of a cell, death of a targeted cell, alteration of cell phenotype or physiology, slowing of cellular growth, sensitization to a second therapy, sensitization to a particular therapy, and the like.

Methods include identifying a cell or patient in need of inducing those cellular characteristics. Also, it will be understood that an amount of a synthetic nucleic acid that is provided to a cell or organism is an "effective amount," which refers to an amount needed (or a sufficient amount) to achieve a desired goal, such as inducing a particular cellular characteristic(s). Certain embodiments of the methods include providing or introducing to a cell a nucleic acid molecule corresponding to a mature miRNA in the cell in an amount effective to achieve a desired physiological result.

Moreover, methods can involve providing synthetic or nonsynthetic miRNA molecules. It is contemplated that in these embodiments, that the methods may or may not be limited to providing only one or more synthetic miRNA molecules or only one or more nonsynthetic miRNA molecules. Thus, in certain embodiments, methods may involve providing both synthetic and nonsynthetic miRNA molecules. In this situation, a cell or cells are most likely provided a synthetic miRNA molecule corresponding to a particular miRNA and a nonsynthetic miRNA molecule corresponding to a different miRNA. Furthermore, any method articulated using a list of miRNAs using Markush group language may be articulated without the Markush group language and a disjunctive article (*i.e.*, or) instead, and vice versa.

In some embodiments, there is a method for reducing or inhibiting cell proliferation in a cell comprising introducing into or providing to the cell an effective amount of (i) an miRNA inhibitor molecule or (ii) a synthetic or nonsynthetic miRNA molecule that corresponds to a miRNA sequence. In certain embodiments the methods involves introducing into the cell an effective amount of (i) a miRNA inhibitor molecule having a 5' to 3' sequence that is at least 90% complementary to the 5' to 3' sequence of one or more mature miRNA.

Certain embodiments of the invention include methods of treating a pathologic condition, in particular cancer, *e.g.*, lung or liver cancer. In one aspect, the method comprises contacting a target cell with one or more nucleic acid, synthetic miRNA, or miRNA comprising at least one nucleic acid segment having all or a portion of a miRNA sequence. The segment may be 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30 or more nucleotides or nucleotide analog, including all integers there between. An aspect of the invention includes the modulation of gene expression, miRNA expression or function or mRNA expression or function within a target cell, such as a cancer cell.

Typically, an endogenous gene, miRNA or mRNA is modulated in the cell. In particular embodiments, the nucleic acid sequence comprises at least one segment that is at least 70, 75, 80, 85, 90, 95, or 100% identical in nucleic acid sequence to one or more miRNA or gene sequence. Modulation of the expression or processing of an endogenous gene, miRNA, or mRNA can be through modulation of the processing of a mRNA, such processing including transcription, transportation and/or translation with in a cell. Modulation may also be effected by the inhibition or enhancement of miRNA activity with a cell, tissue, or organ. Such processing may affect the expression of an encoded product or the stability of the mRNA. In still other embodiments, a nucleic acid sequence can comprise a modified nucleic acid sequence. In certain aspects, one or more miRNA sequence may include or comprise a modified nucleobase or nucleic acid sequence.

It will be understood in methods of the invention that a cell or other biological matter such as an organism (including patients) can be provided a miRNA or miRNA molecule corresponding to a particular miRNA by administering to the cell or organism a nucleic acid molecule that functions as the corresponding miRNA once inside the cell. The form of the

molecule provided to the cell may not be the form that acts a miRNA once inside the cell. Thus, it is contemplated that in some embodiments, a synthetic miRNA or a nonsynthetic miRNA is provided such that it becomes processed into a mature and active miRNA once it has access to the cell's miRNA processing machinery. In certain embodiments, it is specifically contemplated that the miRNA molecule provided is not a mature miRNA molecule but a nucleic acid molecule that can be processed into the mature miRNA once it is accessible to miRNA processing machinery. The term "nonsynthetic" in the context of miRNA means that the miRNA is not "synthetic," as defined herein. Furthermore, it is contemplated that in embodiments of the invention that concern the use of synthetic miRNAs, the use of corresponding nonsynthetic miRNAs is also considered an aspect of the invention, and vice versa. It will be understand that the term "providing" an agent is used to include "administering" the agent to a patient.

In certain embodiments, methods also include targeting a miRNA to modulate in a cell or organism. The term "targeting a miRNA to modulate" means a nucleic acid of the invention will be employed so as to modulate the selected miRNA. In some embodiments the modulation is achieved with a synthetic or non-synthetic miRNA that corresponds to the targeted miRNA, which effectively provides the targeted miRNA to the cell or organism (positive modulation). In other embodiments, the modulation is achieved with a miRNA inhibitor, which effectively inhibits the targeted miRNA in the cell or organism (negative modulation).

In some embodiments, the miRNA targeted to be modulated is a miRNA that affects a disease, condition, or pathway. In certain embodiments, the miRNA is targeted because a treatment can be provided by negative modulation of the targeted miRNA. In other embodiments, the miRNA is targeted because a treatment can be provided by positive modulation of the targeted miRNA or its targets.

In certain methods of the invention, there is a further step of administering the selected miRNA modulator to a cell, tissue, organ, or organism (collectively "biological matter") in need of treatment related to modulation of the targeted miRNA or in need of the physiological or biological results discussed herein (such as with respect to a particular cellular pathway or result like decrease in cell viability). Consequently, in some methods of the invention there is a step of identifying a patient in need of treatment that can be provided by the miRNA modulator(s). It is

contemplated that an effective amount of a miRNA modulator can be administered in some embodiments. In particular embodiments, there is a therapeutic benefit conferred on the biological matter, where a "therapeutic benefit" refers to an improvement in the one or more conditions or symptoms associated with a disease or condition or an improvement in the prognosis, duration, or status with respect to the disease. It is contemplated that a therapeutic benefit includes, but is not limited to, a decrease in pain, a decrease in morbidity, a decrease in a symptom. For example, with respect to cancer, it is contemplated that a therapeutic benefit can be inhibition of tumor growth, prevention of metastasis, reduction in number of metastases, inhibition of cancer cell proliferation, induction of cell death in cancer cells, inhibition of angiogenesis near cancer cells, induction of apoptosis of cancer cells, reduction in pain, reduction in risk of recurrence, induction of chemo- or radiosensitivity in cancer cells, prolongation of life, and/or delay of death directly or indirectly related to cancer.

Furthermore, it is contemplated that the miRNA compositions may be provided as part of a therapy to a patient, in conjunction with traditional therapies or preventative agents. Moreover, it is contemplated that any method discussed in the context of therapy may be applied preventatively, particularly in a patient identified to be potentially in need of the therapy or at risk of the condition or disease for which a therapy is needed.

In addition, methods of the invention concern employing one or more nucleic acids corresponding to a miRNA and a therapeutic drug. The nucleic acid can enhance the effect or efficacy of the drug, reduce any side effects or toxicity, modify its bioavailability, and/or decrease the dosage or frequency needed. In certain embodiments, the therapeutic drug is a cancer therapeutic. Consequently, in some embodiments, there is a method of treating cancer in a patient comprising administering to the patient the cancer therapeutic and an effective amount of at least one miRNA molecule that improves the efficacy of the cancer therapeutic or protects non-cancer cells. Cancer therapies also include a variety of combination therapies with both chemical and radiation based treatments. Combination chemotherapies include but are not limited to, for example, 5-fluorouracil, alemtuzumab, amrubicin, bevacizumab, bleomycin, bortezomib, busulfan, camptothecin, capecitabine, carboplatin, cetuximab, chlorambucil, cisplatin (CDDP), COX-2 inhibitors (*e.g.*, celecoxib), cyclophosphamide, cytarabine, dactinomycin, dasatinib, daunorubicin, dexamethasone, docetaxel, doxorubicin (adriamycin),

EGFR inhibitors (gefitinib and cetuximab), erlotinib, estrogen receptor binding agents, etoposide (VP16), everolimus, farnesyl-protein transferase inhibitors, gefitinib, gemcitabine, gemtuzumab, ibritumomab, ifosfamide, imatinib mesylate, larotaxel, lapatinib, lonafarnib, mechlorethamine, melphalan, methotrexate, mitomycin, navelbine, nitrosurea, nocodazole, oxaliplatin, paclitaxel, plicomycin, procarbazine, raloxifene, rituximab, sirolimus, sorafenib, sunitinib, tamoxifen, taxol, taxotere, temsirolimus, tipifarnib, tositumomab, transplatinum, trastuzumab, vinblastin, vincristin, or vinorelbine or any analog or derivative variant of the foregoing.

Generally, inhibitors of miRNAs can be given to decrease the activity of an endogenous miRNA. For example, inhibitors of miRNA molecules that increase cell proliferation can be provided to cells to decrease cell proliferation. The present invention contemplates these embodiments in the context of the different physiological effects observed with the different miRNA molecules and miRNA inhibitors disclosed herein. These include, but are not limited to, the following physiological effects: increase and decreasing cell proliferation, increasing or decreasing apoptosis, increasing transformation, increasing or decreasing cell viability, activating or inhibiting a kinase (*e.g.*, Erk), activating/inducing or inhibiting hTert, inhibit stimulation of growth promoting pathway (*e.g.*, Stat 3 signaling), reduce or increase viable cell number, and increase or decrease number of cells at a particular phase of the cell cycle. Methods of the invention are generally contemplated to include providing or introducing one or more different nucleic acid molecules corresponding to one or more different miRNA molecules. It is contemplated that the following, at least the following, or at most the following number of different nucleic acid or miRNA molecules may be provided or introduced: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, or any range derivable therein. This also applies to the number of different miRNA molecules that can be provided or introduced into a cell.

II. PHARMACEUTICAL FORMULATIONS AND DELIVERY

Methods of the present invention include the delivery of an effective amount of a miRNA or an expression construct encoding the same. An "effective amount" of the pharmaceutical

composition, generally, is defined as that amount sufficient to detectably and repeatedly to achieve the stated desired result, for example, to ameliorate, reduce, minimize or limit the extent of the disease or its symptoms. Other more rigorous definitions may apply, including elimination, eradication or cure of disease.

A. Administration

In certain embodiments, it is desired to kill cells, inhibit cell growth, inhibit metastasis, decrease tumor or tissue size, and/or reverse or reduce the malignant or disease phenotype of cells. The routes of administration will vary, naturally, with the location and nature of the lesion or site to be targeted, and include, *e.g.*, intradermal, subcutaneous, regional, parenteral, intravenous, intramuscular, intranasal, systemic, and oral administration and formulation. Direct injection, intratumoral injection, or injection into tumor vasculature is specifically contemplated for discrete, solid, accessible tumors, or other accessible target areas. Local, regional, or systemic administration also may be appropriate. For tumors of >4 cm, the volume to be administered will be about 4-10 ml (preferably 10 ml), while for tumors of <4 cm, a volume of about 1-3 ml will be used (preferably 3 ml).

Multiple injections delivered as a single dose comprise about 0.1 to about 0.5 ml volumes. Compositions of the invention may be administered in multiple injections to a tumor or a targeted site. In certain aspects, injections may be spaced at approximately 1 cm intervals.

In the case of surgical intervention, the present invention may be used preoperatively, to render an inoperable tumor subject to resection. Alternatively, the present invention may be used at the time of surgery, and/or thereafter, to treat residual or metastatic disease. For example, a resected tumor bed may be injected or perfused with a formulation comprising a miRNA or combinations thereof. Administration may be continued post-resection, for example, by leaving a catheter implanted at the site of the surgery. Periodic post-surgical treatment also is envisioned. Continuous perfusion of an expression construct or a viral construct also is contemplated.

Continuous administration also may be applied where appropriate, for example, where a tumor or other undesired affected area is excised and the tumor bed or targeted site is treated to eliminate residual, microscopic disease. Delivery via syringe or catherization is contemplated.

Such continuous perfusion may take place for a period from about 1-2 hours, to about 2-6 hours, to about 6-12 hours, to about 12-24 hours, to about 1-2 days, to about 1-2 wk or longer following the initiation of treatment. Generally, the dose of the therapeutic composition via continuous perfusion will be equivalent to that given by a single or multiple injections, adjusted over a period of time during which the perfusion occurs.

Treatment regimens may vary as well and often depend on tumor type, tumor location, immune condition, target site, disease progression, and health and age of the patient. Certain tumor types will require more aggressive treatment. The clinician will be best suited to make such decisions based on the known efficacy and toxicity (if any) of the therapeutic formulations.

In certain embodiments, the tumor or affected area being treated may not, at least initially, be resectable. Treatments with compositions of the invention may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection may serve to eliminate microscopic residual disease at the tumor or targeted site.

Treatments may include various "unit doses." A unit dose is defined as containing a predetermined quantity of a therapeutic composition(s). The quantity to be administered, and the particular route and formulation, are within the skill of those in the clinical arts. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time. With respect to a viral component of the present invention, a unit dose may conveniently be described in terms of μg or mg of miRNA or miRNA mimetic. Alternatively, the amount specified may be the amount administered as the average daily, average weekly, or average monthly dose.

miRNA can be administered to the patient in a dose or doses of about or of at least about 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930,

940, 950, 960, 970, 980, 990, 1000 μg or mg, or more, or any range derivable therein. Alternatively, the amount specified may be the amount administered as the average daily, average weekly, or average monthly dose, or it may be expressed in terms of mg/kg, where kg refers to the weight of the patient and the mg is specified above. In other embodiments, the amount specified is any number discussed above but expressed as mg/m^2 (with respect to tumor size or patient surface area).

B. Injectable Compositions and Formulations

In some embodiments, the method for the delivery of a miRNA or an expression construct encoding such or combinations thereof is via systemic administration. However, the pharmaceutical compositions disclosed herein may also be administered parenterally, subcutaneously, directly, intratracheally, intravenously, intradermally, intramuscularly, or even intraperitoneally as described in U.S. Patents 5,543,158, 5,641,515, and 5,399,363 (each specifically incorporated herein by reference in its entirety).

Injection of nucleic acids may be delivered by syringe or any other method used for injection of a solution, as long as the nucleic acid and any associated components can pass through the particular gauge of needle required for injection. A syringe system has also been described for use in gene therapy that permits multiple injections of predetermined quantities of a solution precisely at any depth (U.S. Patent 5,846,225).

Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U.S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium

containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In certain formulations, a water-based formulation is employed while in others, it may be lipid-based. In particular embodiments of the invention, a composition comprising a tumor suppressor protein or a nucleic acid encoding the same is in a water-based formulation. In other embodiments, the formulation is lipid based.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, intratumoral, intralesional, and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

As used herein, a "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents,

buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

The nucleic acid(s) are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective. The quantity to be administered depends on the subject to be treated, including, *e.g.*, the aggressiveness of the disease or cancer, the size of any tumor(s) or lesions, the previous or other courses of treatment. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner. Suitable regimes for initial administration and subsequent administration are also variable, but are typified by an initial administration followed by other administrations. Such administration may be systemic, as a single dose, continuous over a period of time spanning 10, 20, 30, 40, 50, 60 minutes, and/or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or more hours, and/or 1, 2, 3, 4, 5, 6, 7, days or more. Moreover, administration may be through a time release or sustained release mechanism, implemented by formulation and/or mode of administration.

C. Combination Treatments

In certain embodiments, the compositions and methods of the present invention involve a miRNA, or expression construct encoding such. These miRNA compositions can be used in combination with a second therapy to enhance the effect of the miRNA therapy, or increase the therapeutic effect of another therapy being employed. These compositions would be provided in a combined amount effective to achieve the desired effect, such as the killing of a cancer cell and/or the inhibition of cellular hyperproliferation. This process may involve contacting the cells with the miRNA or second therapy at the same or different time. This may be achieved by contacting the cell with one or more compositions or pharmacological formulation that includes or more of the agents, or by contacting the cell with two or more distinct compositions or

formulations, wherein one composition provides (1) miRNA; and/or (2) a second therapy. A second composition or method may be administered that includes a chemotherapy, radiotherapy, surgical therapy, immunotherapy or gene therapy.

It is contemplated that one may provide a patient with the miRNA therapy and the second therapy within about 12-24 h of each other and, more preferably, within about 6-12 h of each other. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

In certain embodiments, a course of treatment will last 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 days or more. It is contemplated that one agent may be given on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, and/or 90, any combination thereof, and another agent is given on day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, and/or 90, or any combination thereof. Within a single day (24-hour period), the patient may be given one or multiple administrations of the agent(s). Moreover, after a course of treatment, it is contemplated that there is a period of time at which no treatment is administered. This time period may last 1, 2, 3, 4, 5, 6, 7 days, and/or 1, 2, 3, 4, 5 weeks, and/or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months or more, depending on the condition of the patient, such as their prognosis, strength, health, etc.

Various combinations may be employed, for example miRNA therapy is "A" and a second therapy is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B

B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

Administration of any compound or therapy of the present invention to a patient will follow general protocols for the administration of such compounds, taking into account the toxicity, if any, of the vector or any protein or other agent. Therefore, in some embodiments there is a step of monitoring toxicity that is attributable to combination therapy. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, as well as surgical intervention, may be applied in combination with the described therapy.

In specific aspects, it is contemplated that a second therapy, such as chemotherapy, radiotherapy, immunotherapy, surgical therapy or other gene therapy, is employed in combination with the miRNA therapy, as described herein.

1. Chemotherapy

A wide variety of chemotherapeutic agents may be used in accordance with the present invention. The term "chemotherapy" refers to the use of drugs to treat cancer. A "chemotherapeutic agent" is used to connote a compound or composition that is administered in the treatment of cancer. These agents or drugs are categorized by their mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent may be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis. Most chemotherapeutic agents fall into the following categories: alkylating agents, antimetabolites, antitumor antibiotics, mitotic inhibitors, and nitrosoureas.

a. Alkylating agents

Alkylating agents are drugs that directly interact with genomic DNA to prevent the cancer cell from proliferating. This category of chemotherapeutic drugs represents agents that affect all phases of the cell cycle, that is, they are not phase-specific. Alkylating agents can be implemented to treat chronic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and particular cancers of the breast, lung, and ovary. They include: busulfan,

chlorambucil, cisplatin, cyclophosphamide (cytoxan), dacarbazine, ifosfamide, mechlorethamine (mustargen), and melphalan. Troglitazaone can be used to treat cancer in combination with any one or more of these alkylating agents.

b. Antimetabolites

Antimetabolites disrupt DNA and RNA synthesis. Unlike alkylating agents, they specifically influence the cell cycle during S phase. They have been used to combat chronic leukemias in addition to tumors of breast, ovary and the gastrointestinal tract. Antimetabolites include 5-fluorouracil (5-FU), cytarabine (Ara-C), fludarabine, gemcitabine, and methotrexate.

5-Fluorouracil (5-FU) has the chemical name of 5-fluoro-2,4(1H,3H)-pyrimidinedione. Its mechanism of action is thought to be by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid. Thus, 5-FU interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and proliferation, it is thought that the effect of 5-FU is to create a thymidine deficiency leading to cell death. Thus, the effect of 5-FU is found in cells that rapidly divide, a characteristic of metastatic cancers.

c. Antitumor Antibiotics

Antitumor antibiotics have both antimicrobial and cytotoxic activity. These drugs also interfere with DNA by chemically inhibiting enzymes and mitosis or altering cellular membranes. These agents are not phase specific so they work in all phases of the cell cycle. Thus, they are widely used for a variety of cancers. Examples of antitumor antibiotics include bleomycin, dactinomycin, daunorubicin, doxorubicin (Adriamycin), and idarubicin, some of which are discussed in more detail below. Widely used in clinical setting for the treatment of neoplasms, these compounds are administered through bolus injections intravenously at doses ranging from 25-75 mg/m^2 at 21 day intervals for adriamycin, to 35-100 mg/m^2 for etoposide intravenously or orally.

d. Mitotic Inhibitors

Mitotic inhibitors include plant alkaloids and other natural agents that can inhibit either protein synthesis required for cell division or mitosis. They operate during a specific phase

during the cell cycle. Mitotic inhibitors comprise docetaxel, etoposide (VP16), paclitaxel, taxol, taxotere, vinblastine, vincristine, and vinorelbine.

e. Nitrosureas

Nitrosureas, like alkylating agents, inhibit DNA repair proteins. They are used to treat non-Hodgkin's lymphomas, multiple myeloma, malignant melanoma, in addition to brain tumors. Examples include carmustine and lomustine.

2. Radiotherapy

Radiotherapy, also called radiation therapy, is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, normal cells are able to repair themselves and function properly. Radiotherapy may be used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, or cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

Radiation therapy used according to the present invention may include, but is not limited to, the use of γ-rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated such as microwaves, proton beam irradiation (U.S. Patents 5,760,395 and 4,870,287) and UV-irradiation. It is most likely that all of these factors affect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 wk), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells. Radiotherapy may comprise the use of radiolabeled antibodies to deliver doses of radiation directly to the cancer site (radioimmunotherapy). Once injected into the body, the antibodies actively seek out the cancer cells, which are destroyed by the cell-killing (cytotoxic) action of the radiation. This approach can minimize the risk of radiation damage to healthy cells.

Stereotactic radio-surgery (gamma knife) for brain and other tumors does not use a knife, but very precisely targeted beams of gamma radiotherapy from hundreds of different angles. Only one session of radiotherapy, taking about four to five hours, is needed. For this treatment a specially made metal frame is attached to the head. Then, several scans and x-rays are carried out to find the precise area where the treatment is needed. During the radiotherapy for brain tumors, the patient lies with their head in a large helmet, which has hundreds of holes in it to allow the radiotherapy beams through. Related approaches permit positioning for the treatment of tumors in other areas of the body.

3. Immunotherapy

In the context of cancer treatment, immunotherapeutics, generally, rely on the use of immune effector cells and molecules to target and destroy cancer cells. Trastuzumab (Herceptin™) is such an example. The immune effector may be, for example, an antibody specific for some marker on the surface of a tumor cell. The antibody alone may serve as an effector of therapy or it may recruit other cells to actually affect cell killing. The antibody also may be conjugated to a drug or toxin (chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, etc.) and serve merely as a targeting agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells. The combination of therapeutic modalities, *i.e.*, direct cytotoxic activity and inhibition or reduction of ErbB2 would provide therapeutic benefit in the treatment of ErbB2 overexpressing cancers.

In one aspect of immunotherapy, the tumor or disease cell must bear some marker that is amenable to targeting, *i.e.*, is not present on the majority of other cells. Many tumor markers exist and any of these may be suitable for targeting in the context of the present invention. Common tumor markers include carcinoembryonic antigen, prostate specific antigen, urinary tumor associated antigen, fetal antigen, tyrosinase (p97), gp68, TAG-72, HMFG, Sialyl Lewis Antigen, MucA, MucB, PLAP, estrogen receptor, laminin receptor, erb B and p155. An alternative aspect of immunotherapy is to combine anticancer effects with immune stimulatory effects. Immune stimulating molecules also exist including: cytokines such as IL-2, IL-4, IL-12, GM-CSF, gamma-IFN, chemokines such as MIP-1, MCP-1, IL-8 and growth factors such as FLT3 ligand. Combining immune stimulating molecules, either as proteins or using gene

delivery in combination with a tumor suppressor such as MDA-7 has been shown to enhance anti-tumor effects (Ju *et al.*, 2000). Moreover, antibodies against any of these compounds can be used to target the anti-cancer agents discussed herein.

Examples of immunotherapies currently under investigation or in use are immune adjuvants *e.g.*, *Mycobacterium bovis*, *Plasmodium falciparum*, dinitrochlorobenzene and aromatic compounds (U.S. Patents 5,801,005 and 5,739,169; Hui and Hashimoto, 1998; Christodoulides *et al.*, 1998), cytokine therapy *e.g.*, interferons α, β and γ; IL-1, GM-CSF and TNF (Bukowski *et al.*, 1998; Davidson *et al.*, 1998; Hellstrand *et al.*, 1998) gene therapy *e.g.*, TNF, IL-1, IL-2, p53 (Qin *et al.*, 1998; Austin-Ward and Villaseca, 1998; U.S. Patents 5,830,880 and 5,846,945) and monoclonal antibodies *e.g.*, anti-ganglioside GM2, anti-HER-2, anti-p185; Pietras *et al.*, 1998; Hanibuchi *et al.*, 1998; U.S. Patent 5,824,311). Herceptin (trastuzumab) is a chimeric (mouse-human) monoclonal antibody that blocks the HER2-neu receptor. It possesses anti-tumor activity and has been approved for use in the treatment of malignant tumors (Dillman, 1999). Table 5 is a non-limiting list of several known anti-cancer immunotherapeutic agents and their targets. It is contemplated that one or more of these therapies may be employed with the miRNA therapies described herein.

A number of different approaches for passive immunotherapy of cancer exist. They may be broadly categorized into the following: injection of antibodies alone; injection of antibodies coupled to toxins or chemotherapeutic agents; injection of antibodies coupled to radioactive isotopes; injection of anti-idiotype antibodies; and finally, purging of tumor cells in bone marrow.

TABLE 5 Examples of known anti-cancer immunotherapeutic agents and their targets

Generic Name	Target
Cetuximab	EGFR
Panitumumab	EGFR
Trastuzumab	erbB2 receptor
Bevacizumab	VEGF
Alemtuzumab	CD52
Gemtuzumab ozogamicin	CD33
Rituximab	CD20
Tositumomab	CD20
Matuzumab	EGFR
Ibritumomab tiuxetan	CD20
Tositumomab	CD20
HuPAM4	MUC1
MORAb-009	Mesothelin
G250	carbonic anhydrase IX
mAb 8H9	8H9 antigen
M195	CD33
Ipilimumab	CTLA4
HuLuc63	CS1
Alemtuzumab	CD53
Epratuzumab	CD22
BC8	CD45
HuJ591	Prostate specific membrane antigen
hA20	CD20
Lexatumumab	TRAIL receptor-2
Pertuzumab	HER-2 receptor
Mik-beta-1	IL-2R
RAV12	RAAG12
SGN-30	CD30
AME-133v	CD20
HeFi-1	CD30
BMS-663513	CD137
Volociximab	anti-α5β1 integrin
GC1008	TGFβ
HCD122	CD40
Siplizumab	CD2
MORAb-003	Folate receptor alpha
CNTO 328	IL-6
MDX-060	CD30
Ofatumumab	CD20
SGN-33	CD33

4. Gene Therapy

In yet another embodiment, a combination treatment involves gene therapy in which a therapeutic polynucleotide is administered before, after, or at the same time as one or more therapeutic miRNA. Delivery of a therapeutic polypeptide or encoding nucleic acid in conjunction with a miRNA may have a combined therapeutic effect on target tissues. A variety of proteins are encompassed within the invention, some of which are described below. Various

genes that may be targeted for gene therapy of some form in combination with the present invention include, but are not limited to inducers of cellular proliferation, inhibitors of cellular proliferation, regulators of programmed cell death, cytokines and other therapeutic nucleic acids or nucleic acid that encode therapeutic proteins.

The tumor suppressor oncogenes function to inhibit excessive cellular proliferation. The inactivation of these genes destroys their inhibitory activity, resulting in unregulated proliferation. The tumor suppressors (*e.g.*, therapeutic polypeptides) p53, FHIT, p16 and C-CAM can be employed.

In addition to p53, another inhibitor of cellular proliferation is p16. The major transitions of the eukaryotic cell cycle are triggered by cyclin-dependent kinases, or CDK's. One CDK, cyclin-dependent kinase 4 (CDK4), regulates progression through the G1. The activity of this enzyme may be to phosphorylate Rb at late G1. The activity of CDK4 is controlled by an activating subunit, D-type cyclin, and by an inhibitory subunit, the p16INK4 has been biochemically characterized as a protein that specifically binds to and inhibits CDK4, and thus may regulate Rb phosphorylation (Serrano *et al.*, 1993; Serrano *et al.*, 1995). Since the p16INK4 protein is a CDK4 inhibitor (Serrano, 1993), deletion of this gene may increase the activity of CDK4, resulting in hyperphosphorylation of the Rb protein. p16 also is known to regulate the function of CDK6.

p16INK4 belongs to a newly described class of CDK-inhibitory proteins that also includes p16B, p19, p21WAF1, and p27KIP1. The p16INK4 gene maps to 9p21, a chromosome region frequently deleted in many tumor types. Homozygous deletions and mutations of the p16INK4 gene are frequent in human tumor cell lines. This evidence suggests that the p16INK4 gene is a tumor suppressor gene. This interpretation has been challenged, however, by the observation that the frequency of the p16INK4 gene alterations is much lower in primary uncultured tumors than in cultured cell lines (Caldas *et al.*, 1994; Cheng *et al.*, 1994; Hussussian *et al.*, 1994; Kamb *et al.*, 1994; Mori *et al.*, 1994; Okamoto *et al.*, 1994; Nobori *et al.*, 1995; Orlow *et al.*, 1994; Arap *et al.*, 1995). Restoration of wild-type p16INK4 function by transfection with a plasmid expression vector reduced colony formation by some human cancer cell lines (Okamoto, 1994; Arap, 1995).

Other genes that may be employed according to the present invention include Rb, APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, zac1, p73, VHL, MMAC1 / PTEN, DBCCR-1, FCC, rsk-3, p27, p27/p16 fusions, p21/p27 fusions, anti-thrombotic genes (*e.g.*, COX-1, TFPI), PGS, Dp, E2F, ras, myc, neu, raf, erb, fms, trk, ret, gsp, hst, abl, E1A, p300, genes involved in angiogenesis (*e.g.*, VEGF, FGF, thrombospondin, BAI-1, GDAIF, or their receptors) and MCC.

5. Surgery

Approximately 60% of persons with cancer will undergo surgery of some type, which includes preventative, diagnostic or staging, curative and palliative surgery. Curative surgery is a cancer treatment that may be used in conjunction with other therapies, such as the treatment of the present invention, chemotherapy, radiotherapy, hormonal therapy, gene therapy, immunotherapy and/or alternative therapies.

Curative surgery includes resection in which all or part of cancerous tissue is physically removed, excised, and/or destroyed. Tumor resection refers to physical removal of at least part of a tumor. In addition to tumor resection, treatment by surgery includes laser surgery, cryosurgery, electrosurgery, and microscopically controlled surgery (Mohs' surgery). It is further contemplated that the present invention may be used in conjunction with removal of superficial cancers, precancers, or incidental amounts of normal tissue.

Upon excision of part of all of cancerous cells, tissue, or tumor, a cavity may be formed in the body. Treatment may be accomplished by perfusion, direct injection or local application of the area with an additional anti-cancer therapy. Such treatment may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. These treatments may be of varying dosages as well.

6. Other Agents

It is contemplated that other agents may be used in combination with the present invention to improve the therapeutic efficacy of treatment. These additional agents include immunomodulatory agents, agents that affect the upregulation of cell surface receptors and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion, agents that increase the sensitivity of the hyperproliferative cells to apoptotic inducers, or other biological agents.

Immunomodulatory agents include tumor necrosis factor; interferon alpha, beta, and gamma; IL-2 and other cytokines; F42K and other cytokine analogs; or MIP-1, MIP-1beta, MCP-1, RANTES, and other chemokines. It is further contemplated that the upregulation of cell surface receptors or their ligands such as Fas / Fas ligand, DR4 or DR5 / TRAIL (Apo-2 ligand) would potentiate the apoptotic inducing abilities of the present invention by establishment of an autocrine or paracrine effect on hyperproliferative cells. Increases intercellular signaling by elevating the number of GAP junctions would increase the anti-hyperproliferative effects on the neighboring hyperproliferative cell population. In other embodiments, cytostatic or differentiation agents can be used in combination with the present invention to improve the anti-hyperproliferative efficacy of the treatments. Inhibitors of cell adhesion are contemplated to improve the efficacy of the present invention. Examples of cell adhesion inhibitors are focal adhesion kinase (FAKs) inhibitors and Lovastatin. It is further contemplated that other agents that increase the sensitivity of a hyperproliferative cell to apoptosis, such as the antibody c225, could be used in combination with the present invention to improve the treatment efficacy.

Apo2 ligand (Apo2L, also called TRAIL) is a member of the tumor necrosis factor (TNF) cytokine family. TRAIL activates rapid apoptosis in many types of cancer cells, yet is not toxic to normal cells. TRAIL mRNA occurs in a wide variety of tissues. Most normal cells appear to be resistant to TRAIL's cytotoxic action, suggesting the existence of mechanisms that can protect against apoptosis induction by TRAIL. The first receptor described for TRAIL, called death receptor 4 (DR4), contains a cytoplasmic "death domain"; DR4 transmits the apoptosis signal carried by TRAIL. Additional receptors have been identified that bind to TRAIL. One receptor, called DR5, contains a cytoplasmic death domain and signals apoptosis much like DR4. The DR4 and DR5 mRNAs are expressed in many normal tissues and tumor cell lines. Recently, decoy receptors such as DcR1 and DcR2 have been identified that prevent TRAIL from inducing apoptosis through DR4 and DR5. These decoy receptors thus represent a novel mechanism for regulating sensitivity to a pro-apoptotic cytokine directly at the cell's surface. The preferential expression of these inhibitory receptors in normal tissues suggests that TRAIL may be useful as an anticancer agent that induces apoptosis in cancer cells while sparing normal cells. (Marsters *et al.*, 1999).

There have been many advances in the therapy of cancer following the introduction of cytotoxic chemotherapeutic drugs. However, one of the consequences of chemotherapy is the development/acquisition of drug-resistant phenotypes and the development of multiple drug resistance. The development of drug resistance remains a major obstacle in the treatment of such tumors and therefore, there is an obvious need for alternative approaches such as gene therapy.

Another form of therapy for use in conjunction with chemotherapy, radiation therapy or biological therapy includes hyperthermia, which is a procedure in which a patient's tissue is exposed to high temperatures (up to 106°F). External or internal heating devices may be involved in the application of local, regional, or whole-body hyperthermia. Local hyperthermia involves the application of heat to a small area, such as a tumor. Heat may be generated externally with high-frequency waves targeting a tumor from a device outside the body. Internal heat may involve a sterile probe, including thin, heated wires or hollow tubes filled with warm water, implanted microwave antennae, or radiofrequency electrodes.

A patient's organ or a limb is heated for regional therapy, which is accomplished using devices that produce high energy, such as magnets. Alternatively, some of the patient's blood may be removed and heated before being perfused into an area that will be internally heated. Whole-body heating may also be implemented in cases where cancer has spread throughout the body. Warm-water blankets, hot wax, inductive coils, and thermal chambers may be used for this purpose.

Hormonal therapy may also be used in conjunction with the present invention or in combination with any other cancer therapy previously described. The use of hormones may be employed in the treatment of certain cancers such as breast, prostate, ovarian, or cervical cancer to lower the level or block the effects of certain hormones such as testosterone or estrogen. This treatment is often used in combination with at least one other cancer therapy as a treatment option or to reduce the risk of metastases.

This application incorporates U.S. Application Serial No. 11/349,727 filed on February 8, 2006 claiming priority to U.S. Provisional Application Serial No. 60/650,807 filed February 8, 2005 herein by references in its entirety.

III. MIRNA MOLECULES

MicroRNA molecules ("miRNAs") are generally 21 to 22 nucleotides in length, though lengths of 19 and up to 23 nucleotides have been reported. The miRNAs are each processed from a longer precursor RNA molecule ("precursor miRNA"). Precursor miRNAs are transcribed from non-protein-encoding genes. The precursor miRNAs have two regions of complementarity that enables them to form a stem-loop- or fold-back-like structure, which is cleaved in animals by a ribonuclease III-like nuclease enzyme called Dicer. The processed miRNA is typically a portion of the stem.

The processed miRNA (also referred to as "mature miRNA") becomes part of a large complex to down-regulate a particular target gene or its gene product.. Examples of animal miRNAs include those that imperfectly basepair with the target, which halts translation (Olsen *et al.*, 1999; Seggerson *et al.*, 2002). siRNA molecules also are processed by Dicer, but from a long, double-stranded RNA molecule. siRNAs are not naturally found in animal cells, but they can direct the sequence-specific cleavage of an mRNA target through a RNA-induced silencing complex (RISC) (Denli *et al.*, 2003).

A. Array Preparation

Certain embodiments of the present invention concerns the preparation and use of mRNA or nucleic acid arrays, miRNA or nucleic acid arrays, and/or miRNA or nucleic acid probe arrays, which are macroarrays or microarrays of nucleic acid molecules (probes) that are fully or nearly complementary (over the length of the prove) or identical (over the length of the prove) to a plurality of nucleic acid, mRNA or miRNA molecules, precursor miRNA molecules, or nucleic acids derived from the various genes and gene pathways modulated by miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or mmu-miR-292-3p miRNAs and that are positioned on a support or support material in a spatially separated organization. Macroarrays are typically sheets of nitrocellulose or nylon upon which probes have been spotted. Microarrays position the nucleic acid probes more densely such that up to 10,000 nucleic acid molecules can be fit into a region typically 1 to 4 square centimeters. Microarrays can be fabricated by spotting nucleic acid molecules, *e.g.*, genes, oligonucleotides, *etc.*, onto substrates or fabricating oligonucleotide sequences *in situ* on a substrate. Spotted or fabricated nucleic acid

molecules can be applied in a high density matrix pattern of up to about 30 non-identical nucleic acid molecules per square centimeter or higher, *e.g.* up to about 100 or even 1000 per square centimeter. Microarrays typically use coated glass as the solid support, in contrast to the nitrocellulose-based material of filter arrays. By having an ordered array of marker RNA and/or miRNA-complementing nucleic acid samples, the position of each sample can be tracked and linked to the original sample.

A variety of different array devices in which a plurality of distinct nucleic acid probes are stably associated with the surface of a solid support are known to those of skill in the art. Useful substrates for arrays include nylon, glass, metal, plastic, latex, and silicon. Such arrays may vary in a number of different ways, including average probe length, sequence or types of probes, nature of bond between the probe and the array surface, *e.g.* covalent or non-covalent, and the like. The labeling and screening methods of the present invention and the arrays are not limited in its utility with respect to any parameter except that the probes detect miRNA, or genes or nucleic acid representative of genes; consequently, methods and compositions may be used with a variety of different types of nucleic acid arrays.

Representative methods and apparatus for preparing a microarray have been described, for example, in U.S. Patents 5,143,854; 5,202,231; 5,242,974; 5,288,644; 5,324,633; 5,384,261; 5,405,783; 5,412,087; 5,424,186; 5,429,807; 5,432,049; 5,436,327; 5,445,934; 5,468,613; 5,470,710; 5,472,672; 5,492,806; 5,525,464; 5,503,980; 5,510,270; 5,525,464; 5,527,681; 5,529,756; 5,532,128; 5,545,531; 5,547,839; 5,554,501; 5,556,752; 5,561,071; 5,571,639; 5,580,726; 5,580,732; 5,593,839; 5,599,695; 5,599,672; 5,610;287; 5,624,711; 5,631,134; 5,639,603; 5,654,413; 5,658,734; 5,661,028; 5,665,547; 5,667,972; 5,695,940; 5,700,637; 5,744,305; 5,800,992; 5,807,522; 5,830,645; 5,837,196; 5,871,928; 5,847,219; 5,876,932; 5,919,626; 6,004,755; 6,087,102; 6,368,799; 6,383,749; 6,617,112; 6,638,717; 6,720,138, as well as WO 93/17126; WO 95/11995; WO 95/21265; WO 95/21944; WO 95/35505; WO 96/31622; WO 97/10365; WO 97/27317; WO 99/35505; WO 09923256; WO 09936760; WO0138580; WO 0168255; WO 03020898; WO 03040410; WO 03053586; WO 03087297; WO 03091426; WO03100012; WO 04020085; WO 04027093; EP 373 203; EP 785 280; EP 799 897 and UK 8 803 000; the disclosures of which are all herein incorporated by reference.

It is contemplated that the arrays can be high density arrays, such that they contain 2, 20, 25, 50, 80, 100 or more different probes. It is contemplated that they may contain 1000, 16,000, 65,000, 250,000 or 1,000,000 or more different probes. The probes can be directed to mRNA and/or miRNA targets in one or more different organisms or cell types. The oligonucleotide probes range from 5 to 50, 5 to 45, 10 to 40, 9 to 34, or 15 to 40 nucleotides in length in some embodiments. In certain embodiments, the oligonucleotide probes are 5, 10, 15, 20 to 20, 25, 30, 35, 40 nucleotides in length including all integers and ranges there between.

The location and sequence of each different probe sequence in the array are generally known. Moreover, the large number of different probes can occupy a relatively small area providing a high density array having a probe density of generally greater than about 60, 100, 600, 1000, 5,000, 10,000, 40,000, 100,000, or 400,000 different oligonucleotide probes per cm^2. The surface area of the array can be about or less than about 1, 1.6, 2, 3, 4, 5, 6, 7, 8, 9, or 10 cm^2.

Moreover, a person of ordinary skill in the art could readily analyze data generated using an array. Such protocols are disclosed above, and include information found in WO 9743450; WO 03023058; WO 03022421; WO 03029485; WO 03067217; WO 03066906; WO 03076928; WO 03093810; WO 03100448A1, all of which are specifically incorporated by reference.

B. Sample Preparation

It is contemplated that the RNA and/or miRNA of a wide variety of samples can be analyzed using the arrays, index of probes, or array technology of the invention. While endogenous miRNA is contemplated for use with compositions and methods of the invention, recombinant miRNA - including nucleic acids that are complementary or identical to endogenous miRNA or precursor miRNA - can also be handled and analyzed as described herein. Samples may be biological samples, in which case, they can be from biopsy, fine needle aspirates, exfoliates, blood, tissue, organs, semen, saliva, tears, other bodily fluid, hair follicles, skin, or any sample containing or constituting biological cells, particularly cancer or hyperproliferative cells. In certain embodiments, samples may be, but are not limited to, biopsy, or cells purified or enriched to some extent from a biopsy or other bodily fluids or tissues. Alternatively, the sample

may not be a biological sample, but be a chemical mixture, such as a cell-free reaction mixture (which may contain one or more biological enzymes).

C. Hybridization

After an array or a set of probes is prepared and/or the nucleic acid in the sample or probe is labeled, the population of target nucleic acids is contacted with the array or probes under hybridization conditions, where such conditions can be adjusted, as desired, to provide for an optimum level of specificity in view of the particular assay being performed. Suitable hybridization conditions are well known to those of skill in the art and reviewed in Sambrook *et al.* (2001) and WO 95/21944. Of particular interest in many embodiments is the use of stringent conditions during hybridization. Stringent conditions are known to those of skill in the art.

It is specifically contemplated that a single array or set of probes may be contacted with multiple samples. The samples may be labeled with different labels to distinguish the samples. For example, a single array can be contacted with a tumor tissue sample labeled with Cy3, and normal tissue sample labeled with Cy5. Differences between the samples for particular miRNAs corresponding to probes on the array can be readily ascertained and quantified.

The small surface area of the array permits uniform hybridization conditions, such as temperature regulation and salt content. Moreover, because of the small area occupied by the high density arrays, hybridization may be carried out in extremely small fluid volumes (*e.g.*, about 250 μl or less, including volumes of about or less than about 5, 10, 25, 50, 60, 70, 80, 90, 100 μl, or any range derivable therein). In small volumes, hybridization may proceed very rapidly.

D. Differential Expression Analyses

Arrays of the invention can be used to detect differences between two samples. Specifically contemplated applications include identifying and/or quantifying differences between miRNA or gene expression from a sample that is normal and from a sample that is not normal, between a disease or condition and a cell not exhibiting such a disease or condition, or between two differently treated samples. Also, miRNA or gene expression may be compared between a sample believed to be susceptible to a particular disease or condition and one believed

to be not susceptible or resistant to that disease or condition. A sample that is not normal is one exhibiting phenotypic or genotypic trait(s) of a disease or condition, or one believed to be not normal with respect to that disease or condition. It may be compared to a cell that is normal with respect to that disease or condition. Phenotypic traits include symptoms of, or susceptibility to, a disease or condition of which a component is or may or may not be genetic, or caused by a hyperproliferative or neoplastic cell or cells.

An array comprises a solid support with nucleic acid probes attached to the support. Arrays typically comprise a plurality of different nucleic acid probes that are coupled to a surface of a substrate in different, known locations. These arrays, also described as "microarrays" or colloquially "chips" have been generally described in the art, for example, U.S. Patents 5,143,854, 5,445,934, 5,744,305, 5,677,195, 6,040,193, 5,424,186 and Fodor *et al.*, (1991), each of which is incorporated by reference in its entirety for all purposes. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Patent 5,384,261, incorporated herein by reference in its entirety for all purposes. Although a planar array surface is used in certain aspects, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be nucleic acids on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate, see U.S. Patents 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992, which are hereby incorporated in their entirety for all purposes. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all inclusive device, see for example, U.S. Patents 5,856,174 and 5,922,591 incorporated in their entirety by reference for all purposes. See also U.S. Patent Application Ser. No. 09/545,207, filed April 7, 2000 for additional information concerning arrays, their manufacture, and their characteristics, which is incorporated by reference in its entirety for all purposes.

Particularly, arrays can be used to evaluate samples with respect to pathological condition such as cancer and related conditions. It is specifically contemplated that the invention can be used to evaluate differences between stages or sub-classifications of disease, such as between benign, cancerous, and metastatic tissues or tumors.

Phenotypic traits to be assessed include characteristics such as longevity, morbidity, expected survival, susceptibility or receptivity to particular drugs or therapeutic treatments (drug efficacy), and risk of drug toxicity. Samples that differ in these phenotypic traits may also be evaluated using the compositions and methods described.

In certain embodiments, miRNA and/or expression profiles may be generated to evaluate and correlate those profiles with pharmacokinetics or therapies. For example, these profiles may be created and evaluated for patient tumor and blood samples prior to the patient's being treated or during treatment to determine if there are miRNA or genes whose expression correlates with the outcome of the patient's treatment. Identification of differential miRNAs or genes can lead to a diagnostic assay for evaluation of tumor and/or blood samples to determine what drug regimen the patient should be provided. In addition, it can be used to identify or select patients suitable for a particular clinical trial. If an expression profile is determined to be correlated with drug efficacy or drug toxicity, that profile is relevant to whether that patient is an appropriate patient for receiving a drug, for receiving a combination of drugs, or for a particular dosage of the drug.

In addition to the above prognostic assay, samples from patients with a variety of diseases can be evaluated to determine if different diseases can be identified based on miRNA and/or related gene expression levels. A diagnostic assay can be created based on the profiles that doctors can use to identify individuals with a disease or who are at risk to develop a disease. Alternatively, treatments can be designed based on miRNA profiling. Examples of such methods and compositions are described in the U.S. Provisional Patent Application entitled "Methods and Compositions Involving miRNA and miRNA Inhibitor Molecules" filed on May 23, 2005 in the names of David Brown, Lance Ford, Angie Cheng and Rich Jarvis, which is hereby incorporated by reference in its entirety.

E. Other Assays

In addition to the use of arrays and microarrays, it is contemplated that a number of different assays could be employed to analyze miRNAs or related genes, their activities, and their effects. Such assays include, but are not limited to, nucleic acid amplification, polymerase chain reaction, quantitative PCR, RT-PCR, *in situ* hybridization, Northern hybridization,

hybridization protection assay (HPA)(GenProbe), branched DNA (bDNA) assay (Chiron), rolling circle amplification (RCA), single molecule hybridization detection (US Genomics), Invader assay (ThirdWave Technologies), and/or Bridge Litigation Assay (Genaco).

IV. NUCLEIC ACIDS

The present invention concerns nucleic acids, modified nucleic acids, nucleic acid mimetics, miRNAs, mRNAs, genes, and representative fragments thereof that can be labeled, used in array analysis, or employed in diagnostic, therapeutic, or prognostic applications, particularly those related to pathological conditions such as cancer. The molecules may have been endogenously produced by a cell, or been synthesized or produced chemically or recombinantly. They may be isolated and/or purified. Each of the miRNAs described herein include the corresponding SEQ ID NO and accession numbers for these miRNA sequences. The name of a miRNA is often abbreviated and referred to without a "hsa-" prefix and will be understood as such, depending on the context. Unless otherwise indicated, miRNAs referred to in the application are human sequences identified as miR-X or let-X, where X is a number and/or letter.

In certain aspects, a miRNA probe designated by a suffix "5P" or "3P" can be used. "5P" indicates that the mature miRNA derives from the 5' end of the precursor and a corresponding "3P" indicates that it derives from the 3' end of the precursor, as described on the world wide web at sanger.ac.uk. Moreover, in some embodiments, a miRNA probe is used that does not correspond to a known human miRNA. It is contemplated that these non-human miRNA probes may be used in embodiments of the invention or that there may exist a human miRNA that is homologous to the non-human miRNA. In other embodiments, any mammalian cell, biological sample, or preparation thereof may be employed.

In some embodiments of the invention, methods and compositions involving miRNA may concern miRNA, markers (mRNAs), and/or other nucleic acids. Nucleic acids may be, be at least, or be at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101,

102, 103, 104, 105, 106, 107, 108, 109, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides, or any range derivable therein, in length. Such lengths cover the lengths of processed miRNA, miRNA probes, precursor miRNA, miRNA containing vectors, mRNA, mRNA probes, control nucleic acids, and other probes and primers.

In many embodiments, miRNA are 19-24 nucleotides in length, while miRNA probes are 19-35 nucleotides in length, depending on the length of the processed miRNA and any flanking regions added. miRNA precursors are generally between 62 and 110 nucleotides in humans.

Nucleic acids of the invention may have regions of identity or complementarity to another nucleic acid. It is contemplated that the region of complementarity or identity can be at least 5 contiguous residues, though it is specifically contemplated that the region is, is at least, or is at most 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 contiguous nucleotides. It is further understood that the length of complementarity within a precursor miRNA or other nucleic acid or between a miRNA probe and a miRNA or a miRNA gene are such lengths. Moreover, the complementarity may be expressed as a percentage, meaning that the complementarity between a probe and its target is 90% or greater over the length of the probe. In some embodiments, complementarity is or is at least 90%, 95% or 100%. In particular, such lengths may be applied to any nucleic acid comprising a nucleic acid sequence identified in any of SEQ ID NOs described herein, accession number, or any other sequence disclosed herein. Typically, the

commonly used name of the miRNA is given (with its identifying source in the prefix, for example, "hsa" for human sequences) and the processed miRNA sequence. Unless otherwise indicated, a miRNA without a prefix will be understood to refer to a human miRNA. Moreover, a lowercase letter in a miRNA name may or may not be lowercase; for example, hsa-mir-130b can also be referred to as miR-130B. The term "miRNA probe" refers to a nucleic acid probe that can identify a particular miRNA or structurally related miRNAs.

It is understood that some nucleic acids are derived from genomic sequences or a gene. In this respect, the term "gene" is used for simplicity to refer to the genomic sequence encoding the precursor nucleic acid or miRNA for a given miRNA or gene. However, embodiments of the invention may involve genomic sequences of a miRNA that are involved in its expression, such as a promoter or other regulatory sequences.

The term "recombinant" may be used and this generally refers to a molecule that has been manipulated *in vitro* or that is a replicated or expressed product of such a molecule.

The term "nucleic acid" is well known in the art. A "nucleic acid" as used herein will generally refer to a molecule (one or more strands) of DNA, RNA or a derivative or analog thereof, comprising a nucleobase. A nucleobase includes, for example, a naturally occurring purine or pyrimidine base found in DNA (*e.g.*, an adenine "A," a guanine "G," a thymine "T" or a cytosine "C") or RNA (*e.g.*, an A, a G, an uracil "U" or a C). The term "nucleic acid" encompasses the terms "oligonucleotide" and "polynucleotide," each as a subgenus of the term "nucleic acid."

The term "miRNA" generally refers to a single-stranded molecule, but in specific embodiments, molecules implemented in the invention will also encompass a region or an additional strand that is partially (between 10 and 50% complementary across length of strand), substantially (greater than 50% but less than 100% complementary across length of strand) or fully complementary to another region of the same single-stranded molecule or to another nucleic acid. Thus, miRNA nucleic acids may encompass a molecule that comprises one or more complementary or self-complementary strand(s) or "complement(s)" of a particular sequence. For example, precursor miRNA may have a self-complementary region, which is up to 100% complementary. miRNA probes or nucleic acids of the invention can include, can be or

can be at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99 or 100% complementary to their target.

It is understood that a "synthetic nucleic acid" of the invention means that the nucleic acid does not have all or part of a chemical structure or sequence of a naturally occurring nucleic acid. Consequently, it will be understood that the term "synthetic miRNA" refers to a "synthetic nucleic acid" that functions in a cell or under physiological conditions as a naturally occurring miRNA.

While embodiments of the invention may involve synthetic miRNAs or synthetic nucleic acids, in some embodiments of the invention, the nucleic acid molecule(s) need not be "synthetic." In certain embodiments, a non-synthetic nucleic acid or miRNA employed in methods and compositions of the invention may have the entire sequence and structure of a naturally occurring mRNA or miRNA precursor or the mature mRNA or miRNA. For example, non-synthetic miRNAs used in methods and compositions of the invention may not have one or more modified nucleotides or nucleotide analogs. In these embodiments, the non-synthetic miRNA may or may not be recombinantly produced. In particular embodiments, the nucleic acid in methods and/or compositions of the invention is specifically a synthetic miRNA and not a non-synthetic miRNA (that is, not a miRNA that qualifies as "synthetic"); though in other embodiments, the invention specifically involves a non-synthetic miRNA and not a synthetic miRNA. Any embodiments discussed with respect to the use of synthetic miRNAs can be applied with respect to non-synthetic miRNAs, and *vice versa*.

It will be understood that the term "naturally occurring" refers to something found in an organism without any intervention by a person; it could refer to a naturally-occurring wildtype or mutant molecule. In some embodiments a synthetic miRNA molecule does not have the sequence of a naturally occurring miRNA molecule. In other embodiments, a synthetic miRNA molecule may have the sequence of a naturally occurring miRNA molecule, but the chemical structure of the molecule, particularly in the part unrelated specifically to the precise sequence (non-sequence chemical structure) differs from chemical structure of the naturally occurring miRNA molecule with that sequence. In some cases, the synthetic miRNA has both a sequence and non-sequence chemical structure that are not found in a naturally-occurring miRNA.

Moreover, the sequence of the synthetic molecules will identify which miRNA is effectively being provided or inhibited; the endogenous miRNA will be referred to as the "corresponding miRNA." Corresponding miRNA sequences that can be used in the context of the invention include, but are not limited to, all or a portion of those sequences in the SEQ IDs provided herein, as well as any other miRNA sequence, miRNA precursor sequence, or any sequence complementary thereof. In some embodiments, the sequence is or is derived from or contains all or part of a sequence identified herein to target a particular miRNA (or set of miRNAs) that can be used with that sequence. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260 or any number or range of sequences there between may be selected to the exclusion of all non-selected sequences.

As used herein, "hybridization", "hybridizes" or "capable of hybridizing" is understood to mean the forming of a double or triple stranded molecule or a molecule with partial double or triple stranded nature. The term "anneal" as used herein is synonymous with "hybridize." The term "hybridization", "hybridize(s)" or "capable of hybridizing" encompasses the terms "stringent condition(s)" or "high stringency" and the terms "low stringency" or "low stringency condition(s)."

As used herein "stringent condition(s)" or "high stringency" are those conditions that allow hybridization between or within one or more nucleic acid strand(s) containing complementary sequence(s), but preclude hybridization of random sequences. Stringent conditions tolerate little, if any, mismatch between a nucleic acid and a target strand. Such conditions are well known to those of ordinary skill in the art, and are preferred for applications requiring high selectivity. Non-limiting applications include isolating a nucleic acid, such as a gene or a nucleic acid segment thereof, or detecting at least one specific mRNA transcript or a nucleic acid segment thereof, and the like.

Stringent conditions may comprise low salt and/or high temperature conditions, such as provided by about 0.02 M to about 0.5 M NaCl at temperatures of about 42°C to about 70°C. It is understood that the temperature and ionic strength of a desired stringency are determined in part by the length of the particular nucleic acid(s), the length and nucleobase content of the target

sequence(s), the charge composition of the nucleic acid(s), and to the presence or concentration of formamide, tetramethylammonium chloride or other solvent(s) in a hybridization mixture.

It is also understood that these ranges, compositions and conditions for hybridization are mentioned by way of non-limiting examples only, and that the desired stringency for a particular hybridization reaction is often determined empirically by comparison to one or more positive or negative controls. Depending on the application envisioned it is preferred to employ varying conditions of hybridization to achieve varying degrees of selectivity of a nucleic acid towards a target sequence. In a non-limiting example, identification or isolation of a related target nucleic acid that does not hybridize to a nucleic acid under stringent conditions may be achieved by hybridization at low temperature and/or high ionic strength. Such conditions are termed "low stringency" or "low stringency conditions," and non-limiting examples of low stringency include hybridization performed at about 0.15 M to about 0.9 M NaCl at a temperature range of about 20°C to about 50°C. Of course, it is within the skill of one in the art to further modify the low or high stringency conditions to suite a particular application.

A. Nucleobase, Nucleoside, Nucleotide, and Modified Nucleotides

As used herein a "nucleobase" refers to a heterocyclic base, such as for example a naturally occurring nucleobase (*i.e.*, an A, T, G, C or U) found in at least one naturally occurring nucleic acid (*i.e.*, DNA and RNA), and naturally or non-naturally occurring derivative(s) and analogs of such a nucleobase. A nucleobase generally can form one or more hydrogen bonds ("anneal" or "hybridize") with at least one naturally occurring nucleobase in a manner that may substitute for naturally occurring nucleobase pairing (*e.g.*, the hydrogen bonding between A and T, G and C, and A and U).

"Purine" and/or "pyrimidine" nucleobase(s) encompass naturally occurring purine and/or pyrimidine nucleobases and also derivative(s) and analog(s) thereof, including but not limited to, those a purine or pyrimidine substituted by one or more of an alkyl, caboxyalkyl, amino, hydroxyl, halogen (*i.e.*, fluoro, chloro, bromo, or iodo), thiol or alkylthiol moiety. Preferred alkyl (*e.g.*, alkyl, caboxyalkyl, *etc.*) moieties comprise of from about 1, about 2, about 3, about 4, about 5, to about 6 carbon atoms. Other non-limiting examples of a purine or pyrimidine include a deazapurine, a 2,6-diaminopurine, a 5-fluorouracil, a xanthine, a hypoxanthine, a 8-

bromoguanine, a 8-chloroguanine, a bromothymine, a 8-aminoguanine, a 8-hydroxyguanine, a 8-methylguanine, a 8-thioguanine, an azaguanine, a 2-aminopurine, a 5-ethylcytosine, a 5-methylcyosine, a 5-bromouracil, a 5-ethyluracil, a 5-iodouracil, a 5-chlorouracil, a 5-propyluracil, a thiouracil, a 2-methyladenine, a methylthioadenine, a N,N-diemethyladenine, an azaadenines, a 8-bromoadenine, a 8-hydroxyadenine, a 6-hydroxyaminopurine, a 6-thiopurine, a 4-(6-aminohexyl/cytosine), and the like. Other examples are well known to those of skill in the art.

As used herein, a "nucleoside" refers to an individual chemical unit comprising a nucleobase covalently attached to a nucleobase linker moiety. A non-limiting example of a "nucleobase linker moiety" is a sugar comprising 5-carbon atoms (*i.e.*, a "5-carbon sugar"), including but not limited to a deoxyribose, a ribose, an arabinose, or a derivative or an analog of a 5-carbon sugar. Non-limiting examples of a derivative or an analog of a 5-carbon sugar include a 2'-fluoro-2'-deoxyribose or a carbocyclic sugar where a carbon is substituted for an oxygen atom in the sugar ring. Different types of covalent attachment(s) of a nucleobase to a nucleobase linker moiety are known in the art (Kornberg and Baker, 1992).

As used herein, a "nucleotide" refers to a nucleoside further comprising a "backbone moiety". A backbone moiety generally covalently attaches a nucleotide to another molecule comprising a nucleotide, or to another nucleotide to form a nucleic acid. The "backbone moiety" in naturally occurring nucleotides typically comprises a phosphorus moiety, which is covalently attached to a 5-carbon sugar. The attachment of the backbone moiety typically occurs at either the 3'- or 5'-position of the 5-carbon sugar. However, other types of attachments are known in the art, particularly when a nucleotide comprises derivatives or analogs of a naturally occurring 5-carbon sugar or phosphorus moiety.

A nucleic acid may comprise, or be composed entirely of, a derivative or analog of a nucleobase, a nucleobase linker moiety and/or backbone moiety that may be present in a naturally occurring nucleic acid. RNA with nucleic acid analogs may also be labeled according to methods of the invention. As used herein a "derivative" refers to a chemically modified or altered form of a naturally occurring molecule, while the terms "mimic" or "analog" refer to a molecule that may or may not structurally resemble a naturally occurring molecule or moiety,

but possesses similar functions. As used herein, a "moiety" generally refers to a smaller chemical or molecular component of a larger chemical or molecular structure. Nucleobase, nucleoside and nucleotide analogs or derivatives are well known in the art, and have been described (see for example, Scheit, 1980, incorporated herein by reference).

Additional non-limiting examples of nucleosides, nucleotides or nucleic acids include those in: U.S. Patents 5,681,947, 5,652,099 and 5,763,167, 5,614,617, 5,670,663, 5,872,232, 5,859,221, 5,446,137, 5,886,165, 5,714,606, 5,672,697, 5,466,786, 5,792,847, 5,223,618, 5,470,967, 5,378,825, 5,777,092, 5,623,070, 5,610,289, 5,602,240, 5,858,988, 5,214,136, 5,700,922, 5,708,154, 5,728,525, 5,637,683, 6,251,666, 5,480,980, and 5,728,525, each of which is incorporated herein by reference in its entirety.

Labeling methods and kits of the invention specifically contemplate the use of nucleotides that are both modified for attachment of a label and can be incorporated into a miRNA molecule. Such nucleotides include those that can be labeled with a dye, including a fluorescent dye, or with a molecule such as biotin. Labeled nucleotides are readily available; they can be acquired commercially or they can be synthesized by reactions known to those of skill in the art.

Modified nucleotides for use in the invention are not naturally occurring nucleotides, but instead, refer to prepared nucleotides that have a reactive moiety on them. Specific reactive functionalities of interest include: amino, sulfhydryl, sulfoxyl, aminosulfhydryl, azido, epoxide, isothiocyanate, isocyanate, anhydride, monochlorotriazine, dichlorotriazine, mono-or dihalogen substituted pyridine, mono- or disubstituted diazine, maleimide, epoxide, aziridine, sulfonyl halide, acid halide, alkyl halide, aryl halide, alkylsulfonate, N-hydroxysuccinimide ester, imido ester, hydrazine, azidonitrophenyl, azide, 3-(2-pyridyl dithio)-propionamide, glyoxal, aldehyde, iodoacetyl, cyanomethyl ester, p-nitrophenyl ester, o-nitrophenyl ester, hydroxypyridine ester, carbonyl imidazole, and the other such chemical groups. In some embodiments, the reactive functionality may be bonded directly to a nucleotide, or it may be bonded to the nucleotide through a linking group. The functional moiety and any linker cannot substantially impair the ability of the nucleotide to be added to the miRNA or to be labeled. Representative linking groups include carbon containing linking groups, typically ranging from about 2 to 18, usually

from about 2 to 8 carbon atoms, where the carbon containing linking groups may or may not include one or more heteroatoms, *e.g.* S, O, N etc., and may or may not include one or more sites of unsaturation. Of particular interest in many embodiments are alkyl linking groups, typically lower alkyl linking groups of 1 to 16, usually 1 to 4 carbon atoms, where the linking groups may include one or more sites of unsaturation. The functionalized nucleotides (or primers) used in the above methods of functionalized target generation may be fabricated using known protocols or purchased from commercial vendors, *e.g.*, Sigma, Roche, Ambion, Biosearch Technologies and NEN. Functional groups may be prepared according to ways known to those of skill in the art, including the representative information found in U.S. Patents 4,404,289; 4,405,711; 4,337,063 and 5,268,486, and U.K. Patent 1,529,202, which are all incorporated by reference.

Amine-modified nucleotides are used in several embodiments of the invention. The amine-modified nucleotide is a nucleotide that has a reactive amine group for attachment of the label. It is contemplated that any ribonucleotide (G, A, U, or C) or deoxyribonucleotide (G, A, T, or C) can be modified for labeling. Examples include, but are not limited to, the following modified ribo- and deoxyribo-nucleotides: 5-(3-aminoallyl)-UTP; 8-[(4-amino)butyl]-amino-ATP and 8-[(6-amino)butyl]-amino-ATP; N6-(4-amino)butyl-ATP, N6-(6-amino)butyl-ATP, N4-[2,2-oxy-bis-(ethylamine)]-CTP; N6-(6-Amino)hexyl-ATP; 8-[(6-Amino)hexyl]-amino-ATP; 5-propargylamino-CTP, 5-propargylamino-UTP; 5-(3-aminoallyl)-dUTP; 8-[(4-amino)butyl]-amino-dATP and 8-[(6-amino)butyl]-amino-dATP; N6-(4-amino)butyl-dATP, N6-(6-amino)butyl-dATP, N4-[2,2-oxy-bis-(ethylamine)]-dCTP; N6-(6-Amino)hexyl-dATP; 8-[(6-Amino)hexyl]-amino-dATP; 5-propargylamino-dCTP, and 5-propargylamino-dUTP. Such nucleotides can be prepared according to methods known to those of skill in the art. Moreover, a person of ordinary skill in the art could prepare other nucleotide entities with the same amine-modification, such as a 5-(3-aminoallyl)-CTP, GTP, ATP, dCTP, dGTP, dTTP, or dUTP in place of a 5-(3-aminoallyl)-UTP.

B. Preparation of Nucleic Acids

A nucleic acid may be made by any technique known to one of ordinary skill in the art, such as for example, chemical synthesis, enzymatic production, or biological production. It is specifically contemplated that miRNA probes of the invention are chemically synthesized.

In some embodiments of the invention, miRNAs are recovered or isolated from a biological sample. The miRNA may be recombinant or it may be natural or endogenous to the cell (produced from the cell's genome). It is contemplated that a biological sample may be treated in a way so as to enhance the recovery of small RNA molecules such as miRNA. U.S. Patent Application Serial No. 10/667,126 describes such methods and it is specifically incorporated by reference herein. Generally, methods involve lysing cells with a solution having guanidinium and a detergent.

Alternatively, nucleic acid synthesis is performed according to standard methods. See, for example, Itakura and Riggs (1980) and U.S. Patents 4,704,362, 5,221,619, and 5,583,013, each of which is incorporated herein by reference. Non-limiting examples of a synthetic nucleic acid (*e.g.*, a synthetic oligonucleotide), include a nucleic acid made by *in vitro* chemically synthesis using phosphotriester, phosphite, or phosphoramidite chemistry and solid phase techniques such as described in EP 266,032, incorporated herein by reference, or *via* deoxynucleoside H-phosphonate intermediates as described by Froehler *et al.*, 1986 and U.S. Patent 5,705,629, each incorporated herein by reference. Various different mechanisms of oligonucleotide synthesis have been disclosed in for example, U.S. Patents 4,659,774, 4,816,571, 5,141,813, 5,264,566, 4,959,463, 5,428,148, 5,554,744, 5,574,146, 5,602,244, each of which is incorporated herein by reference.

A non-limiting example of an enzymatically produced nucleic acid include one produced by enzymes in amplification reactions such as PCR™ (see for example, U.S. Patents 4,683,202 and 4,682,195, each incorporated herein by reference), or the synthesis of an oligonucleotide described in U.S. Patent 5,645,897, incorporated herein by reference. See also Sambrook *et al.*, 2001, incorporated herein by reference).

Oligonucleotide synthesis is well known to those of skill in the art. Various different mechanisms of oligonucleotide synthesis have been disclosed in for example, U.S. Patents 4,659,774, 4,816,571, 5,141,813, 5,264,566, 4,959,463, 5,428,148, 5,554,744, 5,574,146, 5,602,244, each of which is incorporated herein by reference.

Recombinant methods for producing nucleic acids in a cell are well known to those of skill in the art. These include the use of vectors (viral and non-viral), plasmids, cosmids, and

other vehicles for delivering a nucleic acid to a cell, which may be the target cell (*e.g.*, a cancer cell) or simply a host cell (to produce large quantities of the desired RNA molecule). Alternatively, such vehicles can be used in the context of a cell free system so long as the reagents for generating the RNA molecule are present. Such methods include those described in Sambrook, 2003, Sambrook, 2001 and Sambrook, 1989, which are hereby incorporated by reference.

C. Isolation of Nucleic Acids

Nucleic acids may be isolated using techniques well known to those of skill in the art, though in particular embodiments, methods for isolating small nucleic acid molecules, and/or isolating RNA molecules can be employed. Chromatography is a process often used to separate or isolate nucleic acids from protein or from other nucleic acids. Such methods can involve electrophoresis with a gel matrix, filter columns, alcohol precipitation, and/or other chromatography. If miRNA from cells is to be used or evaluated, methods generally involve lysing the cells with a chaotropic (*e.g.*, guanidinium isothiocyanate) and/or detergent (*e.g.*, N-lauroyl sarcosine) prior to implementing processes for isolating particular populations of RNA.

In particular methods for separating miRNA from other nucleic acids, a gel matrix is prepared using polyacrylamide, though agarose can also be used. The gels may be graded by concentration or they may be uniform. Plates or tubing can be used to hold the gel matrix for electrophoresis. Usually one-dimensional electrophoresis is employed for the separation of nucleic acids. Plates are used to prepare a slab gel, while the tubing (glass or rubber, typically) can be used to prepare a tube gel. The phrase "tube electrophoresis" refers to the use of a tube or tubing, instead of plates, to form the gel. Materials for implementing tube electrophoresis can be readily prepared by a person of skill in the art or purchased, such as from C.B.S. Scientific Co., Inc. or Scie-Plas.

Methods may involve the use of organic solvents and/or alcohol to isolate nucleic acids, particularly miRNA used in methods and compositions of the invention. Some embodiments are described in U.S. Patent Application Serial No. 10/667,126, which is hereby incorporated by reference. Generally, this disclosure provides methods for efficiently isolating small RNA molecules from cells comprising: adding an alcohol solution to a cell lysate and applying the

alcohol/lysate mixture to a solid support before eluting the RNA molecules from the solid support. In some embodiments, the amount of alcohol added to a cell lysate achieves an alcohol concentration of about 55% to 60%. While different alcohols can be employed, ethanol works well. A solid support may be any structure, and it includes beads, filters, and columns, which may include a mineral or polymer support with electronegative groups. A glass fiber filter or column has worked particularly well for such isolation procedures.

In specific embodiments, miRNA isolation processes include: a) lysing cells in the sample with a lysing solution comprising guanidinium, wherein a lysate with a concentration of at least about 1 M guanidinium is produced; b) extracting miRNA molecules from the lysate with an extraction solution comprising phenol; c) adding to the lysate an alcohol solution for forming a lysate/alcohol mixture, wherein the concentration of alcohol in the mixture is between about 35% to about 70%; d) applying the lysate/alcohol mixture to a solid support; e) eluting the miRNA molecules from the solid support with an ionic solution; and, f) capturing the miRNA molecules. Typically the sample is dried and resuspended in a liquid and volume appropriate for subsequent manipulation.

V. LABELS AND LABELING TECHNIQUES

In some embodiments, the present invention concerns miRNA that are labeled. It is contemplated that miRNA may first be isolated and/or purified prior to labeling. This may achieve a reaction that more efficiently labels the miRNA, as opposed to other RNA in a sample in which the miRNA is not isolated or purified prior to labeling. In many embodiments of the invention, the label is non-radioactive. Generally, nucleic acids may be labeled by adding labeled nucleotides (one-step process) or adding nucleotides and labeling the added nucleotides (two-step process).

A. Labeling Techniques

In some embodiments, nucleic acids are labeled by catalytically adding to the nucleic acid an already labeled nucleotide or nucleotides. One or more labeled nucleotides can be added to miRNA molecules. See U.S. Patent 6,723,509, which is hereby incorporated by reference.

In other embodiments, an unlabeled nucleotide or nucleotides is catalytically added to a miRNA, and the unlabeled nucleotide is modified with a chemical moiety that enables it to be subsequently labeled. In embodiments of the invention, the chemical moiety is a reactive amine such that the nucleotide is an amine-modified nucleotide. Examples of amine-modified nucleotides are well known to those of skill in the art, many being commercially available such as from Ambion, Sigma, Jena Bioscience, and TriLink.

In contrast to labeling of cDNA during its synthesis, the issue for labeling miRNA is how to label the already existing molecule. The present invention concerns the use of an enzyme capable of using a di- or tri-phosphate ribonucleotide or deoxyribonucleotide as a substrate for its addition to a miRNA. Moreover, in specific embodiments, it involves using a modified di- or tri-phosphate ribonucleotide, which is added to the 3' end of a miRNA. Enzymes capable of adding such nucleotides include, but are not limited to, poly(A) polymerase, terminal transferase, and polynucleotide phosphorylase. In specific embodiments of the invention, a ligase is contemplated as not being the enzyme used to add the label, and instead, a non-ligase enzyme is employed. Terminal transferase catalyzes the addition of nucleotides to the 3' terminus of a nucleic acid. Polynucleotide phosphorylase can polymerize nucleotide diphosphates without the need for a primer.

B. Labels

Labels on miRNA or miRNA probes may be colorimetric (includes visible and UV spectrum, including fluorescent), luminescent, enzymatic, or positron emitting (including radioactive). The label may be detected directly or indirectly. Radioactive labels include ^{125}I, ^{32}P, ^{33}P, and ^{35}S. Examples of enzymatic labels include alkaline phosphatase, luciferase, horseradish peroxidase, and β-galactosidase. Labels can also be proteins with luminescent properties, *e.g.*, green fluorescent protein and phycoerythrin.

The colorimetric and fluorescent labels contemplated for use as conjugates include, but are not limited to, Alexa Fluor dyes, BODIPY dyes, such as BODIPY FL; Cascade Blue; Cascade Yellow; coumarin and its derivatives, such as 7-amino-4-methylcoumarin, aminocoumarin and hydroxycoumarin; cyanine dyes, such as Cy3 and Cy5; eosins and erythrosins; fluorescein and its derivatives, such as fluorescein isothiocyanate; macrocyclic

chelates of lanthanide ions, such as Quantum Dye™; Marina Blue; Oregon Green; rhodamine dyes, such as rhodamine red, tetramethylrhodamine and rhodamine 6G; Texas Red; , fluorescent energy transfer dyes, such as thiazole orange-ethidium heterodimer; and, TOTAB.

Specific examples of dyes include, but are not limited to, those identified above and the following: Alexa Fluor 350, Alexa Fluor 405, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 500. Alexa Fluor 514, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 610, Alexa Fluor 633, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, and, Alexa Fluor 750; amine-reactive BODIPY dyes, such as BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/655, BODIPY FL, BODIPY R6G, BODIPY TMR, and, BODIPY-TR; Cy3, Cy5, 6-FAM, Fluorescein Isothiocyanate, HEX, 6-JOE, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, REG, Rhodamine Green, Rhodamine Red, Renographin, ROX, SYPRO, TAMRA, 2',4',5',7'-Tetrabromosulfonefluorescein, and TET.

Specific examples of fluorescently labeled ribonucleotides are available from Molecular Probes, and these include, Alexa Fluor 488-5-UTP, Fluorescein-12-UTP, BODIPY FL-14-UTP, BODIPY TMR-14-UTP, Tetramethylrhodamine-6-UTP, Alexa Fluor 546-14-UTP, Texas Red-5-UTP, and BODIPY TR-14-UTP. Other fluorescent ribonucleotides are available from Amersham Biosciences, such as Cy3-UTP and Cy5-UTP.

Examples of fluorescently labeled deoxyribonucleotides include Dinitrophenyl (DNP)-11-dUTP, Cascade Blue-7-dUTP, Alexa Fluor 488-5-dUTP, Fluorescein-12-dUTP, Oregon Green 488-5-dUTP, BODIPY FL-14-dUTP, Rhodamine Green-5-dUTP, Alexa Fluor 532-5-dUTP, BODIPY TMR-14-dUTP, Tetramethylrhodamine-6-dUTP, Alexa Fluor 546-14-dUTP, Alexa Fluor 568-5-dUTP, Texas Red-12-dUTP, Texas Red-5-dUTP, BODIPY TR-14-dUTP, Alexa Fluor 594-5-dUTP, BODIPY 630/650-14-dUTP, BODIPY 650/665-14-dUTP; Alexa Fluor 488-7-OBEA-dCTP, Alexa Fluor 546-16-OBEA-dCTP, Alexa Fluor 594-7-OBEA-dCTP, Alexa Fluor 647-12-OBEA-dCTP.

It is contemplated that nucleic acids may be labeled with two different labels. Furthermore, fluorescence resonance energy transfer (FRET) may be employed in methods of

the invention (*e.g.*, Klostermeier *et al.*, 2002; Emptage, 2001; Didenko, 2001, each incorporated by reference).

Alternatively, the label may not be detectable *per se*, but indirectly detectable or allowing for the isolation or separation of the targeted nucleic acid. For example, the label could be biotin, digoxigenin, polyvalent cations, chelator groups and the other ligands, include ligands for an antibody.

C. Visualization Techniques

A number of techniques for visualizing or detecting labeled nucleic acids are readily available. Such techniques include, microscopy, arrays, Fluorometry, Light cyclers or other real time PCR machines, FACS analysis, scintillation counters, Phosphoimagers, Geiger counters, MRI, CAT, antibody-based detection methods (Westerns, immunofluorescence, immunohistochemistry), histochemical techniques, HPLC (Griffey *et al.*, 1997), spectroscopy, capillary gel electrophoresis (Cummins *et al.*, 1996), spectroscopy; mass spectroscopy; radiological techniques; and mass balance techniques.

When two or more differentially colored labels are employed, fluorescent resonance energy transfer (FRET) techniques may be employed to characterize association of one or more nucleic acid. Furthermore, a person of ordinary skill in the art is well aware of ways of visualizing, identifying, and characterizing labeled nucleic acids, and accordingly, such protocols may be used as part of the invention. Examples of tools that may be used also include fluorescent microscopy, a BioAnalyzer, a plate reader, Storm (Molecular Dynamics), Array Scanner, FACS (fluorescent activated cell sorter), or any instrument that has the ability to excite and detect a fluorescent molecule.

VI. KITS

Any of the compositions described herein may be comprised in a kit. In a non-limiting example, reagents for isolating miRNA, labeling miRNA, and/or evaluating a miRNA population using an array, nucleic acid amplification, and/or hybridization can be included in a kit, as well reagents for preparation of samples from blood samples. The kit may further include reagents for creating or synthesizing miRNA probes. The kits will thus comprise, in suitable container

means, an enzyme for labeling the miRNA by incorporating labeled nucleotide or unlabeled nucleotides that are subsequently labeled. In certain aspects, the kit can include amplification reagents. In other aspects, the kit may include various supports, such as glass, nylon, polymeric beads, and the like, and/or reagents for coupling any probes and/or target nucleic acids. It may also include one or more buffers, such as reaction buffer, labeling buffer, washing buffer, or a hybridization buffer, compounds for preparing the miRNA probes, and components for isolating miRNA. Other kits of the invention may include components for making a nucleic acid array comprising miRNA, and thus, may include, for example, a solid support.

Kits for implementing methods of the invention described herein are specifically contemplated. In some embodiments, there are kits for preparing miRNA for multi-labeling and kits for preparing miRNA probes and/or miRNA arrays. In these embodiments, kit comprise, in suitable container means, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more of the following: (1) poly(A) polymerase; (2) unmodified nucleotides (G, A, T, C, and/or U); (3) a modified nucleotide (labeled or unlabeled); (4) poly(A) polymerase buffer; and, (5) at least one microfilter; (6) label that can be attached to a nucleotide; (7) at least one miRNA probe; (8) reaction buffer; (9) a miRNA array or components for making such an array; (10) acetic acid; (11) alcohol; (12) solutions for preparing, isolating, enriching, and purifying miRNAs or miRNA probes or arrays. Other reagents include those generally used for manipulating RNA, such as formamide, loading dye, ribonuclease inhibitors, and DNase.

In specific embodiments, kits of the invention include an array containing miRNA probes, as described in the application. An array may have probes corresponding to all known miRNAs of an organism or a particular tissue or organ in particular conditions, or to a subset of such probes. The subset of probes on arrays of the invention may be or include those identified as relevant to a particular diagnostic, therapeutic, or prognostic application. For example, the array may contain one or more probes that is indicative or suggestive of (1) a disease or condition (acute myeloid leukemia), (2) susceptibility or resistance to a particular drug or treatment; (3) susceptibility to toxicity from a drug or substance; (4) the stage of development or severity of a disease or condition (prognosis); and (5) genetic predisposition to a disease or condition.

For any kit embodiment, including an array, there can be nucleic acid molecules that contain or can be used to amplify a sequence that is a variant of, identical to or complementary to all or part of any of SEQ IDs described herein. In certain embodiments, a kit or array of the invention can contain one or more probes for the miRNAs identified by the SEQ IDs described herein. Any nucleic acid discussed above may be implemented as part of a kit.

The components of the kits may be packaged either in aqueous media or in lyophilized form. The container means of the kits will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which a component may be placed, and preferably, suitably aliquoted. Where there is more than one component in the kit (labeling reagent and label may be packaged together), the kit also will generally contain a second, third or other additional container into which the additional components may be separately placed. However, various combinations of components may be comprised in a vial. The kits of the present invention also will typically include a means for containing the nucleic acids, and any other reagent containers in close confinement for commercial sale. Such containers may include injection or blow molded plastic containers into which the desired vials are retained.

When the components of the kit are provided in one and/or more liquid solutions, the liquid solution is an aqueous solution, with a sterile aqueous solution being particularly preferred.

However, the components of the kit may be provided as dried powder(s). When reagents and/or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means. In some embodiments, labeling dyes are provided as a dried power. It is contemplated that 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 120, 130, 140, 150, 160, 170, 180, 190, 200, 300, 400, 500, 600, 700, 800, 900, 1000 μg or at least or at most those amounts of dried dye are provided in kits of the invention. The dye may then be resuspended in any suitable solvent, such as DMSO.

Such kits may also include components that facilitate isolation of the labeled miRNA. It may also include components that preserve or maintain the miRNA or that protect against its degradation. Such components may be RNAse-free or protect against RNAses. Such kits

generally will comprise, in suitable means, distinct containers for each individual reagent or solution.

A kit will also include instructions for employing the kit components as well the use of any other reagent not included in the kit. Instructions may include variations that can be implemented.

Kits of the invention may also include one or more of the following: Control RNA; nuclease-free water; RNase-free containers, such as 1.5 ml tubes; RNase-free elution tubes; PEG or dextran; ethanol; acetic acid; sodium acetate; ammonium acetate; guanidinium; detergent; nucleic acid size marker; RNase-free tube tips; and RNase or DNase inhibitors.

It is contemplated that such reagents are embodiments of kits of the invention. Such kits, however, are not limited to the particular items identified above and may include any reagent used for the manipulation or characterization of miRNA.

VII. EXAMPLES

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-15A

miRNAs are believed to regulate gene expression by binding to target mRNA transcripts and (1) initiating transcript degradation or (2) altering protein translation from the transcript. Translational regulation leading to an up or down change in protein expression may lead to changes in activity and expression of downstream gene products and genes that are in turn regulated by those proteins. These numerous regulatory effects may be revealed as changes in

the global mRNA expression profile. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-15a expression.

Synthetic pre-miR-15a (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1A.

Manipulation of the expression levels of the genes listed in Table 1A represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-15a has a role in the disease.

The mis-regulation of gene expression by hsa-miR-15a (Table 1A) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-15a expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-15a in A549 cells are shown in Table 2A.

These data demonstrate that hsa-miR-15a directly or indirectly affects the expression of several, cellular proliferation-, development-, and cell growth-related genes and thus primarily effects functional pathways related to cellular growth and cellular development. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2A represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-15a has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-15a were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-15a, are shown in Table 3A.

The verified gene targets of hsa-miR-15a in Table 3A represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and growth pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-15a directly or indirectly regulates

the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-15a targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4A. Based on this review of the genes and related pathways that are regulated by miR-15a, introduction of hsa-miR-15a or an anti-hsa-miR-15a into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 2

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-26A

As mentioned above in Example 1, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-26a expression. Synthetic pre-miR-26a (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags,

log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1B.

Manipulation of the expression levels of the genes listed in Table 1B represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-26a has a role in the disease.

The mis-regulation of gene expression by hsa-miR-26a (Table 1B) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-26a expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-26a in A549 cells are shown in Table 2B.

These data demonstrate that hsa-miR-26a directly or indirectly affects the expression of numerous cellular proliferation-, development-, cell growth, and cancer-related genes and thus primarily affects functional pathways related to cancer, cell signaling, cellular growth, and cellular development. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2B represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-26a has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-26a were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.* (2005). The predicted gene targets that exhibited altered mRNA

expression levels in human cancer cells, following transfection with pre-miR hsa-miR-26a, are shown in Table 3B.

The verified gene targets of hsa-miR-26a in Table 3B represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-26a directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-26a targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4B. Based on this review of the genes and related pathways that are regulated by miR-26a, introduction of hsa-miR-26a or an anti-hsa-miR-26a into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 3

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH ANTI-HSA-MIR-31

Microarray gene expression analyses were performed to identify genes that are mis-regulated by inhibition of hsa-miR-31 expression. Synthetic anti-miR-31 (Ambion) or a negative control anti-miRNA (anti-miR-NC1, Ambion cat. no. AM17010) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary

electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on an Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1C.

Manipulation of the expression levels of the genes listed in Table 1C represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-31 has a role in the disease.

The mis-regulation of gene expression by anti-hsa-miR-31 (Table 1C) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by the inhibition of hsa-miR-31 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following inhibition of hsa-miR-31 in A549 cells are shown in Table 2C.

These data demonstrate that hsa-miR-31 directly or indirectly affects primarily cellular development-related genes and thus primarily affects functional pathways related to cellular development. Cellular development has an integral role in the progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2C

represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-31 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-31 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with anti-hsa-miR-31, are shown in Table 3C.

miRNAs are believed to regulate gene expression by binding to target mRNA transcripts and (1) initiating transcript degradation or (2) altering protein translation from the transcript. Inhibition of hsa-miR-31 would likely inhibit degradation of target transcripts. As expected, the inventors observed that the predicted targets of has-miR-31 exhibiting altered mRNA expression upon transfection with anti-hsa-miR-31 all showed an increase in transcript levels. The verified gene targets of hsa-miR-31 in Table 3C represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

EXAMPLE 4

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-145

As mentioned above in Example 1, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-145 expression. Synthetic pre-miR-145 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1D.

Manipulation of the expression levels of the genes listed in Table 1D represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-145 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-145 (Table 1D) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-145 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-145 in A549 cells are shown in Table 2D.

These data demonstrate that hsa-miR-145 directly or indirectly affects the expression of development- and cancer-related genes. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2D represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-145 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-145 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-145, are shown in Table 3D.

The verified gene target of hsa-miR-145 in Table 3D represents a particularly useful candidate for cancer therapy and therapy of other diseases through manipulation of its expression levels.

EXAMPLE 5:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-147

As mentioned above in Example 1, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-147 expression. Synthetic pre-miR-147 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 µl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA

Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1E.

Manipulation of the expression levels of the genes listed in Table 1E represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-147 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-147 (Table 1E) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-147 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-147 in A549 cells are shown in Table 2E.

These data demonstrate that hsa-miR-147 directly or indirectly affects the expression of numerous cellular development-, cell growth-, and cancer-related genes and thus primarily affects functional pathways related to cellular growth and cellular development. Those cellular

processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2E represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-147 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-147 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-147, are shown in Table 3E.

The verified gene targets of hsa-miR-147 in Table 3E represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-147 directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-147 targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4C. Based on this review of the genes and related pathways that are regulated by miR-147, introduction of hsa-miR-147 or an anti-hsa-miR-147 into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 6:

DELIVERY OF SYNTHETIC HSA-MIR-147 INHIBITS PROLIFERATION OF PARENTAL AND METASTATIC LUNG CANCER CELL LINES

The inventors have previously demonstrated that miRNAs described in this application are involved with the regulation of numerous cell activities that represent intervention points for cancer therapy and for therapy of other diseases and disorders (U.S. Patent Applications serial number 11/141,707 filed May 31, 2005 and serial number 11/273,640 filed November 14, 2005, each incorporated herein by reference in its entirety). For example, overexpression of hsa-miR-147 decreases the proliferation and/or viability of certain normal or cancerous cell lines.

The development of effective therapeutic regimes typically involves demonstrating efficacy and utility of the therapeutic in various cancer models and multiple cancer cell lines that represent the same disease. The inventors assessed the therapeutic effect of hsa-miR-147 for lung cancer by using 11 individual lung cancer cell lines. To measure cellular proliferation of lung cancer cells, the following parental non-small cell lung cancer (NSCLC) cells were used: cells derived from lung adenocarcinoma (A549, H1299, H522, H838, Calu-3, HCC827, HCC2935), cells derived from lung squamous cell carcinoma (H520, H226), cells derived from lung adenosquamous cell carcinoma (H596), cells derived from lung bronchioalveolar carcinoma (H1650), and cells derived from lung large cell carcinoma (H460). In addition to these parental cell lines, highly metastatic NSCLC cells were used that stably express the firefly luciferase gene: A549-luc, H460-luc, HCC827-luc, H1650-luc, H441-luc. Unlike the parental cell lines, these metastatic cells readily migrate to distant sites of the test animal and form metastases upon intravenous injection. Synthetic hsa-miR-147 or negative control miRNA was delivered via lipid-based transfection into A549, H1299, H522, H838, Calu-3, HCC827, HCC2935, H520, H596, H1650, H460, A549-luc, H460-luc, HCC827-luc, H1650-luc, H441-luc cells and via electroporation into H226 cells. Lipid-based reverse transfection was carried out in triplicates according to a published protocol and the following parameters: 5000-12000 cells per 96 well, 0.1-0.2 μl lipofectamine2000 (Invitrogen, Carlsbad, CA) in 20 μl OptiMEM (Invitrogen), 30 nM final concentration of miRNA in 100 μl (Ovcharenko *et al.*, 2005). Electroporation of H226 cells was carried out using the BioRad GenePulserXcell™ instrument with the following settings: 5×10^6 cells with 5 μg miRNA in 200 μl OptiMEM, square wave pulse at 250 V for 5 ms. Electroporated H226 cells were seeded at 7000 cells per 96-well in a total volume of 100 μl. All cells except for Calu-3 cells were harvested 72 hours post transfection or electroporation for assessment of cellular proliferation. Calu-3 cells were harvested 10 days post transfection. Proliferation assays were performed using Alamar Blue (Invitrogen) following the manufacturer's instructions. As a control for inhibition of cellular proliferation, siRNA against the motor protein kinesin 11, also known as Eg5, was used. Eg5 is essential for cellular survival of most eukaryotic cells and a lack thereof leads to reduced cell proliferation and cell death (Weil *et al.*, 2002). siEg5 was used in lipid-based transfection following the same experimental parameters that apply to miRNA. The inventors also used the topoisomerase II inhibitor etoposide at a final concentration of 10 μM and 50 μM as an internal standard for the potency of

miRNAs. Etoposide is an FDA-approved topoisomerase II inhibitor in the treatment of lung cancer. IC_{50} values for various lung cancer cells have been reported to range between <1-25 μM for SCLC and NSCLC cells (Tsai *et al.*, 1993; Ohsaki *et al.*, 1992). Values obtained from the Alamar Blue assay were normalized to values from cells treated with negative control miRNA. FIG. 1 and FIG. 2 shows % proliferation of hsa-miR-147 treated cells relative to cells treated with negative control miRNA (= 100%). Standard deviations are indicated in the graphs.

Delivery of hsa-miR-147 inhibits cellular proliferation of the parental lung cancer cells A549, H1299, H522, H838, Calu-3, HCC827, HCC2935, H520, H596, H1650, H460, H226, as well as the metastatic lung cancer cells A549-luc, H460-luc, HCC827-luc, H1650-luc and H441-luc (FIG. 1 and FIG. 2). On average, hsa-miR-147 inhibits cellular proliferation of parental lung cancer cells by 25% (FIG. 1), and inhibits cell growth of metastatic lung cancer cells by 42% (FIG. 2). Hsa-miR-147 has maximal inhibitory activity in Calu-3 and H460-luc cells. The growth-inhibitory activity of hsa-miR-147 is comparable to the one of etoposide at concentrations >10 μM. Since hsa-miR-147 induces a therapeutic response in all lung cancer cell tested, hsa-miR-147 may provide a therapeutic benefit to patients with lung cancer and other malignancies.

The inventors determined sensitivity and specificity of hsa-miR-147 by administering hsa-miR-147 or negative control miRNA at increasing concentrations, ranging from 0 pM to 3 nM. Delivery of miRNA and cellular proliferation of A549 and H1299 cells was assessed as described above. Alamar Blue values were normalized to values obtained from mock-transfected cells (0 pM = 100% proliferation). As shown in FIG. 3, increasing amounts of negative control miRNA had no effect on cellular proliferation of A549 or H1299 cells. In contrast, the growth-inhibitory phenotype of hsa-miR-147 is dose-dependent and correlates with increasing amounts of hsa-miR-147. Hsa-miR-147 induces a therapeutic response at concentrations as low as 300 pM.

EXAMPLE 7:

HSA-MIR-147 IN COMBINATION WITH HSA-MIR-124A, HSA-MIR-126, HSA-LET-7B, HSA-LET-7C OR HSA-LET-7G SYNERGISTICALLY INHIBITS PROLIFERATION OF LUNG CANCER CELL LINES

miRNAs function in multiple pathways controlling multiple cellular processes. Cancer cells frequently show aberrations in several different pathways which determine their oncogenic properties. Therefore, combinations of multiple miRNAs may provide a better therapeutic benefit rather than a single miRNA. The inventors assessed the efficacy of pair-wise miRNA combinations, administering hsa-miR-147 concurrently with hsa-miR-124a, hsa-miR-126, hsa-let7b, hsa-let-7c or hsa-let7g. H460 lung cancer cells were transiently reverse transfected in triplicates with each miRNA at a final concentration of 300 pM, totaling in 600 pM of oligonucleotide. As a negative control, 600 pM of negative control miRNA (pre-miR NC#2, Ambion) was used. To correlate the effect of various combinations with the effect of the sole miRNA, each miRNA at 300 pM was also combined with 300 pM negative control miRNA. Reverse transfection was carried using the following parameters: 7000 cells per 96 well, 0.15 µl lipofectamine2000 (Invitrogen) in 20 µl OptiMEM (Invitrogen), 100 µl total transfection volume. As an internal control for the potency of miRNA, etoposide was added at 10 µM and 50 µM to mock-transfected cells 24 hours after transfection for the following 48 hours. Cells were harvested 72 hours after transfection and subjected to Alamar Blue assays (Invitrogen). Alamar Blue values were normalized to the ones obtained from cells treated with 600 pM negative control miRNA. Data are expressed as % proliferation relative to negative control miRNA-treated cells.

As shown in FIG. 4, transfection of 300 pM hsa-miR-147 reduces proliferation of H460 cells by 23%. Maximal activity of singly administered miRNAs was observed with hsa-miR-124a, diminished cellular proliferation by 30.6%. Additive activity of pair-wise combinations (*e.g.*, hsa-miR-147 plus hsa-miR-124a) is defined as an activity that is greater than the sole activity of each miRNA (*e.g.*, activity of hsa-miR-147 plus hsa-miR-124a > hsa-miR-147 plus NC AND activity of hsa-miR-147 plus hsa-miR-124a > hsa-miR-124a plus NC). Synergistic activity of pair-wise combinations is defined as an activity that is greater than the sum of the sole activity of each miRNA (*e.g.*, activity of hsa-miR-147 plus hsa-miR-124a > SUM [activity of hsa-miR-147 plus NC AND activity of hsa-miR-124a plus NC]). The data suggest that hsa-miR-

147 combined with hsa-let-7b or hsa-let-7c provides an additive effect; combinations of hsa-miR-147 with hsa-miR124a, hsa-miR-126 or hsa-let-7g results in synergistic activity (FIG. 4). In summary, all pair-wise combinations of hsa-miR-147 induce a better therapeutic response in H460 lung cancer cells relative to the administration of the single miRNA.

The combinatorial use of miRNAs represents a potentially useful therapy for cancer and other diseases.

EXAMPLE 8:

DELIVERY OF SYNTHETIC HSA-MIR-147 INHIBITS TUMOR GROWTH OF LUNG CANCER CELLS IN MICE

The inventors assessed the growth-inhibitory activity of hsa-miR-147 in a human lung cancer xenograft grown in immunodeficient mice. Hsa-miR-147 was delivered into A549 lung cancer cells via electroporation using the BioRad GenePulserXcell^{TM} instrument with the following settings: 15×10^6 cells with 5 μg miRNA in 200 μl OptiMEM, square wave pulse at 150 V for 10 ms. A total of 30×10^6 A549 cells was used to 5×10^6 electroporated cells were mixed with matrigel in a 1:1 ratio and injected subcutaneously into the flank of NOD/SCID mice. As a negative control, A549 cells were electroporated with negative control miRNA (pre-miR-NC#2, Ambion) as describe above. NC miRNA-treated cells were injected into the opposite flank of the same animal to control for animal-to-animal variability. A total of 30×10^6 A549 cells per hsa-miR-147 and NC was used to accommodate 5 injections into 5 animals. Size measurements of tumors started 14 days after injection once tumors have reached a measurable size. Length and width of tumors were determined every day for the following 6 days. Tumor volumes were calculated using the formula $V=\text{length}\times\text{width}^2/2$ in which the length is greater than the width. Tumor volumes derived from NC-treated cells and hsa-miR-147-treated cells were averaged and plotted over time (FIG. 5). Standard deviations are shown in the graph. The p value, indicating statistical significance, is shown for values obtained on day 20.

Administration of hsa-miR-147 into the A549 lung cancer xenograft inhibited tumor growth *in vivo* (FIG. 5). Cancer cells that received negative control miRNA developed tumors more rapidly than cells treated with hsa-miR147. Administration of hsa-miR-147 A549 induced

tumor regression and prevented further tumor growth. Data points obtained on day 20 are statistically significant ($p = 0.01357$).

The data suggest that hsa-miR-147 represents a particularly useful candidate in the treatment of lung cancer and potentially other diseases.

EXAMPLE 9:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-188

As mentioned above in previous examples, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-188 expression. Synthetic pre-miR-188 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix

Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1F.

Manipulation of the expression levels of the genes listed in Table 1F represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-188 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-188 (Table 1F) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-188 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-188 in A549 cells are shown in Table 2F.

These data demonstrate that hsa-miR-188 directly or indirectly affects the expression of numerous cellular proliferation-, development-, and cell growth -related genes and thus primarily affects functional pathways related to cellular growth and cellular development. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2F represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-188 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-188 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al,*. (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-188, are shown in Table 3F below.

The verified gene targets of hsa-miR-188 in Table 3F represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-188 directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-188 targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4D. Based on this review of the genes and related pathways that are regulated by miR-188, introduction of hsa-miR-188 or an anti-hsa-miR-188 into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 10:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-215

Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-215 expression. Synthetic pre-miR-215 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 µl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

As mentioned above in previous examples, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 µg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer

2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1G.

Manipulation of the expression levels of the genes listed in Table 1G represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-215 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-215 (Table 1G) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-215 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-215 in A549 cells are shown in Table 2G.

These data demonstrate that hsa-miR-215 directly or indirectly affects the expression of numerous cellular proliferation-, development-, cell growth, and cancer-related genes and thus primarily affects functional pathways related to cellular growth and cellular development. Those cellular processes have integral roles in the development and progression of various cancers.

Manipulation of the expression levels of genes in the cellular pathways shown in Table 2G represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-215 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-215 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.,* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-215, are shown in Table 3G.

The verified gene targets of hsa-miR-215 in Table 3G represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-215 directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-215 targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4E. Based on this review of the genes and related pathways that are regulated by miR-215, introduction of hsa-miR-215 or an anti-hsa-miR-215 into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 11:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-216

As mentioned above in previous examples, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-216 expression. Synthetic pre-miR-216 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the

manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1H.

Manipulation of the expression levels of the genes listed in Table 1H represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-216 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-216 (Table 1H) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-216 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems,

Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-216 in A549 cells are shown in Table 2H.

These data demonstrate that hsa-miR-216 directly or indirectly affects the expression of numerous cellular proliferation-, cellular development-, cell growth-, and cancer-related genes and thus primarily affects functional pathways related to cellular growth and cellular development. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2H represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-216 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-216 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.,* (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-216, are shown in Table 3H.

The verified gene targets of hsa-miR-216 in Table 3H represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-216 directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-216 targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4F. Based on this review of the genes and related pathways that are regulated by miR-216, introduction of hsa-miR216 or an anti-hsa-miR-216 into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 12:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH HSA-MIR-331

As mentioned above in previous examples, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by hsa-miR-331 expression. Synthetic pre-miR-331 (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 μl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 μg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list

of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1I.

Manipulation of the expression levels of the genes listed in Table 1I represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-331 has a role in the disease.

The mis-regulation of gene expression by hsa-miR-331 (Table 1I) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by hsa-miR-331 expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of hsa-miR-331 in A549 cells are shown in Table 2I.

These data demonstrate that hsa-miR-331 directly or indirectly affects the expression of numerous cellular development-, and cancer-related genes and thus primarily affects functional pathways related to cancer and cellular development. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2I represents a potentially useful therapy for cancer and other diseases in which increased or reduced expression of hsa-miR-331 has a role in the disease.

Gene targets for binding of and regulation by hsa-miR-331 were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.*, (2005). The predicted gene targets that exhibited altered mRNA expression levels in human cancer cells, following transfection with pre-miR hsa-miR-331, are shown in Table 3I.

The verified gene targets of hsa-miR-331 in Table 3I represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that hsa-miR-331 directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Hsa-miR-331 targets that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4G. Based on this review of the genes and related pathways that are regulated by miR-331, introduction of hsa-miR-331 or an anti-hsa-miR-331 into a variety of cancer cell types would likely result in a therapeutic response.

EXAMPLE 13:

GENES, GENE PATHWAYS, AND CANCER-RELATED GENES WITH ALTERED EXPRESSION FOLLOWING TRANSFECTION WITH MMU-MIR-292-3P

As mentioned above in previous examples, the regulatory effects of miRNAs are revealed through changes in global gene expression profiles following miRNA expression or inhibition of miRNA expression. Microarray gene expression analyses were performed to identify genes that are mis-regulated by mmu-miR-292-3p expression in human cancer cells. Synthetic pre-miR-292-3p (Ambion) or two negative control miRNAs (pre-miR-NC1, Ambion cat. no. AM17110 and pre-miR-NC2, Ambion, cat. no. AM17111) were reverse transfected into quadruplicate samples of A549 cells for each of three time points. Cells were transfected using siPORT NeoFX (Ambion) according to the manufacturer's recommendations using the following parameters: 200,000 cells per well in a 6 well plate, 5.0 µl of NeoFX, 30 nM final concentration of miRNA in 2.5 ml. Cells were harvested at 4 h, 24 h, and 72 h post transfection. Total RNA was extracted using RNAqueous-4PCR (Ambion) according to the manufacturer's recommended protocol.

mRNA array analyses were performed by Asuragen Services (Austin, TX), according to the company's standard operating procedures. Using the MessageAmp™ II-96 aRNA Amplification Kit (Ambion, cat #1819) 2 µg of total RNA were used for target preparation and labeling with biotin. cRNA yields were quantified using an Agilent Bioanalyzer 2100 capillary electrophoresis protocol. Labeled target was hybridized to Affymetrix mRNA arrays (Human HG-U133A 2.0 arrays) using the manufacturer's recommendations and the following parameters. Hybridizations were carried out at 45°C for 16 hr in an Affymetrix Model 640 hybridization

oven. Arrays were washed and stained on an Affymetrix FS450 Fluidics station, running the wash script Midi_euk2v3_450. The arrays were scanned on a Affymetrix GeneChip Scanner 3000. Summaries of the image signal data, group mean values, p-values with significance flags, log ratios and gene annotations for every gene on the array were generated using the Affymetrix Statistical Algorithm MAS 5.0 (GCOS v1.3). Data were reported in a file (cabinet) containing the Affymetrix data and result files and in files (.cel) containing the primary image and processed cell intensities of the arrays. Data were normalized for the effect observed by the average of two negative control microRNA sequences and then were averaged together for presentation. A list of genes whose expression levels varied by at least 0.7 $\log_2$ from the average negative control was assembled. Results of the microarray gene expression analysis are shown in Table 1J.

The mis-regulation of gene expression in human cancer cells by mmu-miR-292-3p (Table 1J) affects many cellular pathways that represent potential therapeutic targets for the control of cancer and other diseases and disorders. The inventors determined the identity and nature of the cellular genetic pathways affected by the regulatory cascade induced by mmu-miR-292-3p expression. Cellular pathway analyses were performed using Ingenuity Pathways Analysis (Version 4.0, Ingenuity® Systems, Redwood City, CA). Alteration of a given pathway was determined by Fisher's Exact test (Fisher, 1922). The most significantly affected pathways following over-expression of mmu-miR-292-3p in A549 cells are shown in Table 2J.

These data demonstrate that mmu-miR-292-3p directly or indirectly affects the expression of numerous cellular proliferation-, cell development-, cell growth-, and cancer-related genes and thus primarily affects functional pathways, in human cancer cells, that are related to cellular growth and cellular development. Those cellular processes have integral roles in the development and progression of various cancers. Manipulation of the expression levels of genes in the cellular pathways shown in Table 2J represents a potentially useful therapy for cancer and other diseases.

Human gene targets for binding of and regulation by mmu-miR-292-3p were predicted using the proprietary algorithm miRNATarget™ (Asuragen), which is an implementation of the method proposed by Krek *et al.,* (2005). The predicted gene targets that exhibited altered mRNA

expression levels in human cancer cells, following transfection with pre-miR mmu-miR-292-3p, are shown in Table 3J.

The verified gene targets of mmu-miR-292-3p in Table 3J represent particularly useful candidates for cancer therapy and therapy of other diseases through manipulation of their expression levels.

Cell proliferation and survival pathways are commonly altered in tumors (Hanahan and Weinberg, 2000). The inventors have shown that mmu-miR-292-3p directly or indirectly regulates the transcripts of proteins that are critical in the regulation of these pathways. Many of these targets have inherent oncogenic or tumor suppressor activity and are frequently deregulated in human cancer. Human gene targets of mmu-miR-292-3p that have prognostic and/or therapeutic value for the treatment of various malignancies are shown in Table 4H. Based on this review of the genes and related pathways that are regulated by miR-292-3p, introduction of miR-292-3p or an anti-miR-292-3p into a variety of cancer cell types would likely result in a therapeutic response.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

U.S. Patent 4,337,063
U.S. Patent 4,404,289
U.S. Patent 4,405,711
U.S. Patent 4,659,774
U.S. Patent 4,682,195
U.S. Patent 4,683,202
U.S. Patent 4,704,362
U.S. Patent 4,816,571
U.S. Patent 4,870,287
U.S. Patent 4,959,463
U.S. Patent 5,141,813
U.S. Patent 5,143,854
U.S. Patent 5,202,231
U.S. Patent 5,214,136
U.S. Patent 5,221,619
U.S. Patent 5,223,618
U.S. Patent 5,242,974
U.S. Patent 5,264,566
U.S. Patent 5,264,566
U.S. Patent 5,268,486
U.S. Patent 5,288,644
U.S. Patent 5,324,633
U.S. Patent 5,378,825
U.S. Patent 5,384,261
U.S. Patent 5,399,363
U.S. Patent 5,405,783

U.S. Patent 5,412,087
U.S. Patent 5,424,186
U.S. Patent 5,428,148
U.S. Patent 5,429,807
U.S. Patent 5,432,049
U.S. Patent 5,436,327
U.S. Patent 5,445,934
U.S. Patent 5,446,137
U.S. Patent 5,466,468
U.S. Patent 5,466,786
U.S. Patent 5,468,613
U.S. Patent 5,470,710
U.S. Patent 5,470,967
U.S. Patent 5,472,672
U.S. Patent 5,480,980
U.S. Patent 5,492,806
U.S. Patent 5,503,980
U.S. Patent 5,510,270
U.S. Patent 5,525,464
U.S. Patent 5,525,464
U.S. Patent 5,527,681
U.S. Patent 5,529,756
U.S. Patent 5,532,128
U.S. Patent 5,543,158
U.S. Patent 5,545,531
U.S. Patent 5,547,839
U.S. Patent 5,554,501
U.S. Patent 5,554,744
U.S. Patent 5,556,752
U.S. Patent 5,561,071
U.S. Patent 5,571,639

U.S. Patent 5,574,146
U.S. Patent 5,580,726
U.S. Patent 5,580,732
U.S. Patent 5,583,013
U.S. Patent 5,593,839
U.S. Patent 5,599,672
U.S. Patent 5,599,695
U.S. Patent 5,602,240
U.S. Patent 5,602,244
U.S. Patent 5,610,289
U.S. Patent 5,610;287
U.S. Patent 5,614,617
U.S. Patent 5,623,070
U.S. Patent 5,624,711
U.S. Patent 5,631,134
U.S. Patent 5,637,683
U.S. Patent 5,639,603
U.S. Patent 5,641,515
U.S. Patent 5,645,897
U.S. Patent 5,652,099
U.S. Patent 5,654,413
U.S. Patent 5,658,734
U.S. Patent 5,661,028
U.S. Patent 5,665,547
U.S. Patent 5,667,972
U.S. Patent 5,670,663
U.S. Patent 5,672,697
U.S. Patent 5,677,195
U.S. Patent 5,681,947
U.S. Patent 5,695,940
U.S. Patent 5,700,637

U.S. Patent 5,700,922
U.S. Patent 5,705,629
U.S. Patent 5,708,153
U.S. Patent 5,708,154
U.S. Patent 5,714,606
U.S. Patent 5,728,525
U.S. Patent 5,739,169
U.S. Patent 5,744,305
U.S. Patent 5,760,395
U.S. Patent 5,763,167
U.S. Patent 5,770,358
U.S. Patent 5,777,092
U.S. Patent 5,789,162
U.S. Patent 5,792,847
U.S. Patent 5,800,992
U.S. Patent 5,801,005
U.S. Patent 5,807,522
U.S. Patent 5,824,311
U.S. Patent 5,830,645
U.S. Patent 5,830,880
U.S. Patent 5,837,196
U.S. Patent 5,846,225
U.S. Patent 5,846,945
U.S. Patent 5,847,219
U.S. Patent 5,856,174
U.S. Patent 5,858,988
U.S. Patent 5,859,221
U.S. Patent 5,871,928
U.S. Patent 5,872,232
U.S. Patent 5,876,932
U.S. Patent 5,886,165

U.S. Patent 5,919,626
U.S. Patent 5,922,591
U.S. Patent 6,004,755
U.S. Patent 6,040,193
U.S. Patent 6,087,102
U.S. Patent 6,251,666
U.S. Patent 6,368,799
U.S. Patent 6,383,749
U.S. Patent 6,617,112
U.S. Patent 6,638,717
U.S. Patent 6,720,138
U.S. Patent 6,723,509
U.S. Appln. Serial 09/545,207
U.S. Appln. Serial 10/667,126
U.S. Appln. Serial 11/141,707
U.S. Appln. Serial 11/141,707
U.S. Appln. Serial 11/141,707
U.S. Appln. Serial 11/273,640
U.S. Appln. Serial 11/273,640,
U.S. Appln. Serial 11/273,640,
U.S. Appln. Serial 11/349,727
U.S. Prov. Appln. Serial 60/575,743
U.S. Prov. Appln. Serial 60/649,584
U.S. Prov. Appln. Serial 60/650,807

Aaboe *et al.*, Biochim Biophys Acta, 1638(1):72-82, 2003.
Abuharbeid *et al.*, *Int. J. Biochem. Cell Biol.*, 38(9):1463-1468, 2006.
Adams *et al.*, Cancer Lett, 220(2):137-144, 2005.
Adelaide *et al.*, Genes Chromosomes Cancer, 37(4):333-345, 2003.
Akiba *et al.*, *Int. J. Oncol.*, 18(2):257-264, 2001.
Akino *et al.*, Gastroenterology, 129(1):156-169, 2005.

Alevizos *et al.*, Oncogene, 20(43):6196-6204, 2001.

Ambros, Cell, 107(7):823-826, 2001.

Arap *et al., Cancer Res.*, 55(6):1351-1354, 1995.

Aspland *et al.*, Oncogene, 20(40):5708-5717, 2001.

Austin-Ward and Villaseca, *Revista Medica de Chile*, 126(7):838-845, 1998.

Baba *et al.*, Cancer Res, 60(24):6886-6889, 2000.

Bae *et al.*, *J. Biol. Chem.*, 275(33):25255-25261, 2000.

Bagga *et al.*, *Cell*, 122(4):553-563, 2005.

Bai *et al.*, Histol Histopathol, 18(2):449-457, 2003.

Bandyopadhyay *et al.*, Oncogene, 21(22):3541-3551, 2002.

Bangoura *et al.*, World J Gastroenterol, 10(4):525-530, 2004.

Barton *et al.*, Clin Cancer Res, 3(9):1579-1586, 1997.

Bartsch and Tschesche, *FEBS Lett.*, 357(3):255-259, 1995.

Beisner *et al.*, Cancer Res, 66(15):7554-7561, 2006.

Bellovin *et al.*, Oncogene, 25(52):6959-6967, 2006.

Biswas *et al.*, Cancer Res, 64(14):4687-4692, 2004.

Blanc *et al.*, Cancer Lett, 228(1-2):117-123, 2005.

Bodner-Adler *et al.*, Anticancer Res, 21(1B):809-812, 2001.

Boise *et al.*, *Cell*, 74(4):597-608, 1993.

Bostwick *et al.*, *Prostate,* 58(2):164-168, 2004.

Boultwood *et al.*, Br J Haematol, 126(4):508-511, 2004.

Boutros and Byrne, Exp Cell Res, 310(1):152-165, 2005.

Boutros *et al.*, Biochem Biophys Res Commun, 325(4):1115-1121, 2004.

Bradham *et al.*, *J. Cell Biol.,* 114(6):1285-1294, 1991.

Brennecke *et al.*, *Cell*, 113(1):25-36, 2003.

Budhu *et al.*, Cancer Cell, 10(2):99-111, 2006.

Bui *et al.*, Br J Cancer, 77(2):319-324, 1998.

Bukowski *et al., Clinical Cancer Res.*, 4(10):2337-2347, 1998.

Butler *et al.*, Cancer Res, 62(14):4089-4094, 2002.

Cahill *et al.*, Nature, 392(6673):300-303, 1998.

Caldas *et al., Cancer Res.,* 54:3568-3573, 1994.

Calin and Croce, *Nat. Rev. Cancer*, 6(11):857-866, 2006.

Calin *et al.*, *Proc. Natl. Acad. Sci. USA*, 99(24):15524-15529, 2002.

Cao *et al.*, Cell, 107(6):763-775, 2001.

Carbone *et al.*, Blood, 91(3):747-755, 1998.

Carrano *et al.*, Nat Cell Biol, 1(4):193-199, 1999.

Carreiras *et al.*, Gynecol Oncol, 62(2):260-267, 1996.

Carreiras *et al.*, Gynecol Oncol, 72(3):312-322, 1999.

Carrington and Ambros, *Science*, 301(5631):336-338, 2003.

Castillo *et al.*, *Cancer Res.*, 66(12):6129-6138, 2006.

Chan *et al.*, Oncogene, 22(44):6946-6953, 2003.

Chandler *et al.*, *Int. J. Cancer*, 81(3):451-458, 1999.

Chen *et al.*, J Pathol, 200(5):640-646, 2003.

Cheng *et al., Cancer Res.*, 54(21):5547-5551, 1994.

Choi *et al.*, Oncogene, 23(42):7095-7103, 2004.

Cho-Vega *et al.*, *Hum. Pathol.*, 35(9):1095-1100, 2004.

Christodoulides *et al.*, *Microbiology*, 144(Pt 11):3027-3037, 1998.

Ciocca *et al.*, J Natl Cancer Inst, 85(7):570-574, 1993.

Claudio *et al.*, *Clin. Cancer Res.*, 8(6):1808-1815, 2002.

Croci *et al.*, *Cancer Res.*, 64(5):1730-1736, 2004.

Cully *et al.*, Cancer Res, 65(22):10363-10370, 2005.

Cummins *et al.*, In: *IRT: Nucleosides and nucleosides*, La Jolla CA, 72, 1996.

D'Antonio *et al.*, *Int. J. Oncol.*, 21(5):941-948, 2002.

Davalos *et al.*, Oncogene, 26(2):308-311, 2007.

Davidson *et al., J. Immunother.*, 21(5):389-398, 1998.

de Candia *et al.*, Hum Pathol, 37(8):1032-1041, 2006.

de Nigris *et al.*, Cancer Res, 61(5):2267-2275, 2001.

Denli *et al., Trends Biochem. Sci.*, 28:196, 2003.

Didenko, *Biotechniques*, 31(5):1106-1116, 1118, 1120-1121, 2001.

Dillman, *Cancer Biother. Radiopharm.*, 14(1):5-10, 1999.

Dong *et al.*, Crit. Rev. Oncol. Hematol., 54(2):85-93, 2005.

Dong *et al.*, *Mol. Endocrinol.*, 20(10):2315-2325, 2006.

Donnellan and Chetty, Mol Pathol, 51(1):1-7, 1998.

Dyer and Bremner, Nat Rev Cancer, 5(2):91-101, 2005.

Ebert *et al.*, *Cancer Res.*, 54(15):3959-3962, 1994.

Eferl *et al.*, Cell, 112(2):181-192, 2003.

Einama *et al.*, Pancreas, 32(4):376-381, 2006.

Emptage *et al.*, *Neuron*, 29(1):197-208, 2001.

Endoh *et al.*, Br J Cancer, 93(12):1395-1399, 2005.

EP 266,032

EP 373 203

EP 785 280

EP 799 897

Esquela-Kerscher and Slack, *Nat Rev Cancer,* 6(4):259-269, 2006.

Eustace *et al.*, Nat Cell Biol, 6(6):507-514, 2004.

Ezzat *et al.*, *Clin. Cancer Res.*, 11(3):1336-1341, 2005.

Faried *et al.*, Eur J Cancer, 42(10):1455-1465, 2006.

Feldman and Feldman, Nat Rev Cancer, 1(1):34-45, 2001.

Fernandez *et al.*, *Clin. Cancer Res.*, 11(15):5390-5395, 2005.

Fesik, Nat Rev Cancer, 5(11):876-885, 2005.

Filipits *et al.*, Clin Cancer Res, 8(3):729-733, 2002.

Firth and Baxter, *Endocr. Rev.,* 23(6):824-854, 2002.

Fisher, *J. Royal Statistical. Soc.* 85(1):87-94, 1922.

Fleischer *et al.*, *Int. J. Oncol.*, 28(1):25-32, 2006.

Florenes *et al.*, Clin Cancer Res, 6(9):3614-3620, 2000.

Fodor *et al.*, *Biochemistry*, 30(33):8102-8108, 1991.

Froehler *et al.*, *Nucleic Acids Res.*, 14(13):5399-5407, 1986.

Fujiwara *et al.*, Oncogene, 10(5):891-895, 1995.

Furutani *et al.*, *Cancer Lett.,* 122(1-2):209-214, 1998.

Gao *et al.*, Oncol Rep, 17(1):123-128, 2007.

Golay *et al.*, Blood, 87(5):1900-1911, 1996.

Grabsch *et al.*, J Pathol, 200(1):16-22, 2003.

Graff and Zimmer, Clin Exp Metastasis, 20(3):265-273, 2003.

Grandori *et al.*, Annu Rev Cell Dev Biol, 16:653-699, 2000.

Gratas *et al.*, *Cancer Res.*, 58(10):2057-2062, 1998.

Griffey *et al.*, *J. Mass Spectrom*, 32(3):305-13, 1997.

Gstaiger *et al.*, Proc Natl Acad Sci U S A, 98(9):5043-5048, 2001.

Guanti *et al.*, Hum Mol Genet, 9(2):283-287, 2000.

Guo *et al.*, Carcinogenesis, 27(3):454-464, 2006.

Hamamura *et al.*, Proc Natl Acad Sci U S A, 102(31):11041-11046, 2005.

Han *et al.*, Oncogene, 23(7):1333-1341, 2004.

Hanahan and Weinberg, Cell, 100(1):57-70, 2000.

Hanibuchi *et al.*, *Int. J. Cancer*, 78(4):480-485, 1998.

Hannigan *et al.*, Nat Rev Cancer, 5(1):51-63, 2005.

Hartmann *et al.*, Cancer Res, 59(7):1578-1583, 1999.

He *et al.*, *Nature*, 435(7043):828-833, 2005a.

He *et al.*, *Proc. Natl. Acad. Sci. USA*, 102(52):19075-19080, 2005b.

Hellstrand *et al., Acta Oncologica*, 37(4):347-353, 1998.

Hishikawa *et al.*, *J. Biol. Chem.*, 274(52):37461-37466, 1999.

Hooi *et al.*, *Oncogene,* 25(28):3924-3933, 2006.

Houston and O'Connell, *Curr. Opin. Pharmacol.*, 4(4):321-326, 2004.

Huang *et al.*, Clin Cancer Res, 12(2):487-498, 2006.

Huang *et al.*, J Clin Oncol, 23(34):8765-8773, 2005.

Huguet *et al.*, Cancer Res, 54(10):2615-2621, 1994.

Hui and Hashimoto, *Infection Immun.,* 66(11):5329-5336, 1998.

Hussussian *et al.*, *Nat. Genet.*, 8(1):15-21, 1994.

Huusko *et al.*, Nat Genet, 36(9):979-983, 2004.

Hynes and Lane, *Nat. Rev. Cancer*, 5(5):341-354, 2005.

Iolascon *et al.*, Hepatology, 27(4):989-995, 1998.

Ireton and Chen, Curr Cancer Drug Targets, 5(3):149-157, 2005.

Ishikawa *et al.*, Cancer Res, 65(20):9176-9184, 2005.

Ishikawa *et al.*, *Cancer Res.*, 65(20):9176-9184, 2005.

Itakura and Riggs, *Science,* 209:1401-1405, 1980.

Ito *et al.*, Anticancer Res, 21(2A):1043-1048, 2001.

Ito *et al.*, Anticancer Res, 22(3):1581-1584, 2002.

Ito *et al.*, Anticancer Res, 23(3B):2335-2338, 2003b.

Ito *et al.*, Anticancer Res, 25(5):3419-3423, 2005.

Ito *et al.*, *Anticancer Res.*, 23(5A):3819-3824, 2003.

Jaakkola *et al.*, *Int. J. Cancer,* 54(3):378-382, 1993.

Jansen *et al.*, Mol Cancer Ther, 3(2):103-110, 2004.

Jiang *et al.*, Cancer Res, 64(16):5787-5794, 2004.

Jonson *et al.*, Int J Oncol, 19(1):71-81, 2001.

Jonsson *et al.*, Cancer Res, 62(2):409-416, 2002.

Ju *et al., Gene Ther.*, 7(19):1672-1679, 2000.

Jubb *et al.*, Clin Cancer Res, 11(14):5181-5187, 2005.

Kamata *et al.*, J Cancer Res Clin Oncol, 131(9):591-596, 2005.

Kamb *et al.*, *Science*, 2674:436-440, 1994.

Kaufmann *et al.*, *Blood*, 91(3):991-1000, 1998.

Kirikoshi *et al.*, Int J Oncol, 19(1):111-115, 2001.

Kitada *et al.*, *Blood,* 91(9):3379-3389, 1998.

Kitadai *et al.*, *Jpn. J. Cancer Res.*, 84(8):879-884, 1993.

Kleer *et al.*, Clin Cancer Res, 12(15):4485-4490, 2006.

Klostermeier and Millar, *Biopolymers*, 61(3):159-79, 2001-2002.

Koivunen *et al.*, Cancer Lett, 235(1):1-10, 2006.

Kokko *et al.*, BMC Cancer, 6:145, 2006.

Koliopanos *et al.*, *World J. Surg.,* 26(4):420-427, 2002.

Komiya *et al.*, Jpn J Cancer Res, 88(4):389-393, 1997.

Krajewska *et al.*, *Am. J. Pathol.*, 148(5):1567-1576, 1996.

Krasagakis *et al.*, Br J Cancer, 77(9):1492-1494, 1998.

Krek *et al., Nature Genet.* 37:495-500, 2005.

Kulkarni *et al.*, Leukemia, 16(1):127-134, 2002.

Lagos-Quintana *et al.*, *Science,* 294(5543):853-858, 2001.

Lahn and Sundell, Melanoma Res, 14(2):85-89, 2004.

Lambros *et al.*, J Pathol, 205(1):29-40, 2005.

Landen *et al.*, Expert Opin Ther Targets, 9(6):1179-1187, 2005.

Lau *et al.*, *Science,* 294(5543):858-862, 2001.

Lauffart *et al.*, BMC Womens Health, 5:8, 2005.

Lazaris *et al.*, Breast Cancer Res Treat, 43(1):43-51, 1997.

Lazaris *et al.*, Dis Colon Rectum, 38(7):739-745, 1995.

Lee and Ambros, *Science,* 294(5543):862-864, 2001.

Lee *et al.*, Cell Struct Funct, 23(4):193-199, 1998.

Lee *et al.*, *Int. J. Cancer,* 118(10):2490-2497, 2006.

Lee *et al.*, *Oncogene,* 23(39):6672-6676, 2004.

Leprince *et al.*, Nature, 306(5941):395-397, 1983.

Leris *et al.*, Anticancer Res, 25(2A):731-734, 2005.

L'Hote and Knowles, Exp Cell Res, 304(2):417-431, 2005.

Li *et al.*, World J Gastroenterol, 9(2):205-208, 2003.

Liby *et al.*, Folia Biol (Praha), 52(1-2):21-33, 2006.

Lim *et al.,* Nature, 433(7027):769-773, 2005

Lin *et al.*, *Gastroenterology,* 128(1):9-23, 2005.

Liu and Matsuura, *Cell Cycle,* 4(1):63-66, 2005.

Liu *et al.*, *Cancer Res.,* 66(2):653-658, 2006.

Lo Vasco *et al.*, Leukemia, 18(6):1122-1126, 2004.

Lopez-Beltran *et al.*, J Pathol, 209(1):106-113, 2006.

Lu *et al.*, *Nature*, 435(7043):834-838, 2005.

Lucke *et al.*, Cancer Res, 61(2):482-485, 2001.

Mahtouk *et al.*, *Oncogene,* 24(21):3512-3524, 2005.

Maki *et al.*, Proc Natl Acad Sci U S A, 84(9):2848-2852, 1987.

Malumbres and Barbacid, Nat Rev Cancer, 1(3):222-231, 2001.

Markowitz *et al.*, Science, 268(5215):1336-1338, 1995.

Markowitz, Biochim Biophys Acta, 1470(1):M13-20, 2000.

Marks; *Semin. Cancer Biol.*, 16(6):436-443, 2006.

Marsit *et al.*, *Int. J. Cancer,* 119(8):1761-1766, 2006.

Marsters *et al.*, *Recent Prog. Horm. Res.*, 54:225-234, 1999.

Martinez-Lorenzo *et al.*, *Int. J. Cancer*, 75(3):473-481, 1998.

Massague *et al.*, Cell, 103(2):295-309, 2000.

Matsumoto *et al.*, Leukemia, 14(10):1757-1765, 2000.

McGary *et al.*, Cancer Biol Ther, 1(5):459-465, 2002.

Meng *et al., Gastroenterology*, 130:2113-2129, 2006.

Merle *et al.*, Gastroenterology, 127(4):1110-1122, 2004.

Miyake *et al.*, Cancer, 86(2):316-324, 1999.

Mizunuma *et al.*, Br J Cancer, 88(10):1543-1548, 2003.

Moll and Slade, Mol Cancer Res, 2(7):371-386, 2004.

Moller *et al.*, *Int J Cancer*, 57(3):371-377, 1994.

Momand *et al.*, Nucleic Acids Res, 26(15):3453-3459, 1998.

Montero *et al.*, Clin Cancer Res, 4(9):2161-2168, 1998.

Mori *et al., Cancer Res.*, 54(13):3396-3397, 1994.

Mori *et al.*, Gastroenterology, 131(3):797-808, 2006.

Morishita *et al.*, Hepatology, 40(3):677-686, 2004.

Mossink *et al.*, Oncogene, 22(47):7458-7467, 2003.

Nakada *et al.*, Cancer Res, 64(9):3179-3185, 2004.

Nakagawa *et al.*, Oncogene, 23(44):7366-7377, 2004.

Nakayama *et al.*, Cancer, 92(12):3037-3044, 2001.

Nesbit *et al.,* Oncogene, 18(19):3004-3016, 1999.

Nobri *et al.*, *Nature (London)*, 368:753-756, 1995.

Nupponen *et al.*, Am J Pathol, 154(6):1777-1783, 1999.

Nupponen *et al.*, Genes Chromosomes Cancer, 28(2):203-210, 2000.

O' Donnell *et al., Nature*, 435:839-843, 2005.

Ohsaki *et al.*, Cancer Res, 1992. 52(13): p. 3534-8.

Okamoto *et al.*, Hepatology, 38(5):1242-1249, 2003.

Okamoto *et al., Proc. Natl. Acad. Sci. USA*, 91(23):11045-11049, 1994.

Okino *et al.*, Oncol Rep, 13(6):1069-1074, 2005.

Olsen *et al.*, *Dev. Biol.*, 216:671, 1999.

Orlow *et al.*, *Cancer Res,* 54(11):2848-2851, 1994.

Ovcharenko *et al.*, Rna, 2005. 11(6): p. 985-93.

Pan *et al.*, *Neurol. Res.*, 24(7):677-683, 2002.

Parekh *et al.*, Biochem Pharmacol, 63(6):1149-1158, 2002.

PCT Appln. WO 0138580
PCT Appln. WO 0168255
PCT Appln. WO 03020898
PCT Appln. WO 03022421
PCT Appln. WO 03023058
PCT Appln. WO 03029485
PCT Appln. WO 03040410
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PCT Appln. WO 03100012
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PCT Appln. WO 04020085
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PCT Appln. WO 09923256
PCT Appln. WO 09936760
PCT Appln. WO 93/17126
PCT Appln. WO 95/11995
PCT Appln. WO 95/21265
PCT Appln. WO 95/21944
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PCT Appln. WO 95/35505
PCT Appln. WO 96/31622
PCT Appln. WO 97/10365
PCT Appln. WO 97/27317
PCT Appln. WO 9743450
PCT Appln. WO 99/35505

Pennica *et al.*, Proc Natl Acad Sci U S A, 95(25):14717-14722, 1998.

Petit *et al.*, *Genomics*, 57(3):438-441, 1999.

Pietras *et al.*, *Oncogene*, 17(17):2235-2249, 1998.

Prentice *et al.*, Oncogene, 24(49):7281-7289, 2005.

Pruitt *et al., Nucleic Acids Res.*, 33(1):D501-D504, 2005.

Pruneri *et al.*, Clin Cancer Res, 11(1):242-248, 2005.

Qian *et al.*, Proc Natl Acad Sci U S A, 99(23):14925-14930, 2002.

Qin *et al.*, *Proc. Natl. Acad. Sci. USA*, 95(24):14411-14416, 1998.

Ree *et al.*, Cancer Res, 59(18):4675-4680, 1999.

Reimer *et al.*, *J. Biol. Chem.*, 274(16):11022-11029, 1999.

Reinhart *et al.*, Nature, 403(6772):901-906, 2000.

Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580, 1990.

Ritch *et al.*, J Biol Chem, 278(23):20971-20978, 2003.

Romieu-Mourez *et al.*, Cancer Res, 61(9):3810-3818, 2001.

Rossi *et al.*, Cancer Genet Cytogenet, 161(2):97-103, 2005.

Ru *et al.*, Oncogene, 21(30):4673-4679, 2002.

Rubin and Gutmann, Nat Rev Cancer, 5(7):557-564, 2005.

Rust *et al.*, *J. Clin. Pathol.*, 58(5):520-524, 2005.

Ruth *et al.*, J Invest Dermatol, 126(4):862-868, 2006.

Sacchi *et al.*, Science, 231(4736):379-382, 1986.

Saigusa *et al.*, Cancer Sci, 96(10):676-683, 2005.

Saitoh *et al.*, Int J Mol Med, 9(5):515-519, 2002.

Salgia *et al.*, Oncogene, 18(1):67-77, 1999.

Sambrook and Russell, Molecular Cloning: A Laboratory Manual 3rd Ed., Cold Spring Harbor Laboratory Press, 2001.

Sambrook *et al., In: DNA microaarays: a molecular cloning manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2003.

Sanchez-Aguilera *et al.*, Blood, 103(6):2351-2357, 2004.

Sano *et al.*, *Histopathology*, 46(5):532-539, 2005.

Saxena *et al.*, Mol Cell Biochem, 228(1-2):99-104, 2001.

Schulze-Bergkamen *et al.*, *BMC Cancer*, 6:232, 2006.

Seggerson *et al.*, *Dev. Biol.*, 243:215, 2002.

Sementchenko *et al.*, Oncogene, 17(22):2883-2888, 1998.

Serrano *et al.*, *Nature*, 366:704-707, 1993.

Serrano *et al.*, *Science*, 267(5195):249-252, 1995.

Shah *et al.*, *Oncogene*, 21(54):8251-8261, 2002.

Shelly *et al.*, J Biol Chem, 273(17):10496-10505, 1998.

Sherr and McCormick, *Cancer Cell,* 2(2):103-112, 2002.

Shibahara *et al.*, Anticancer Res, 25(3B):1881-1888, 2005.

Shigeishi *et al.*, Oncol Rep, 15(4):933-938, 2006.

Shigemasa *et al.*, *Jpn. J. Cancer Res,* 93(5):542-550, 2002.

Shimo *et al.*, *Cancer Lett.*, 174(1):57-64, 2001.

Shimoyama *et al.*, Clin Cancer Res, 5(5):1125-1130, 1999.

Shin *et al.*, Cancer Lett, 174(2):189-194, 2001.

Shinoura *et al.*, *Cancer Gene Ther.*, 7(2):224-232, 2000.

Sieghart *et al.*, *J. Hepatol.,* 44(1):151-157, 2006.

Simpson and Parsons, Exp Cell Res, 264(1):29-41, 2001.

Simpson *et al.*, Oncogene, 14(18):2149-2157, 1997.

Skotzko *et al.*, *Cancer Res.,* 55(23):5493-5498, 1995.

Solic and Davies, *Exp. Cell Res.,* 234(2):465-476, 1997.

Soufla *et al.*, Cancer Lett, 221(1):105-118, 2005.

Sparmann and Bar-Sagi, *Cancer Cell,* 6(5):447-458, 2004.

Su *et al.*, Clin Cancer Res, 7(5):1320-1324, 2001.

Sui *et al.*, Oncol Rep, 15(4):765-771, 2006.

Takanami, Oncol Rep, 13(4):727-731, 2005.

Takashima *et al.*, Proteomics, 3(12):2487-2493, 2003.

Takimoto *et al.*, *Biochem. Biophys. Res. Commun.*, 251(1):264-268, 1998.

Tan *et al.*, Leuk Res, 27(2):125-131, 2003.

Tanaka *et al.*, Proc Natl Acad Sci U S A, 95(17):10164-10169, 1998.

Tanami *et al.*, Lab Invest, 85(9):1118-1129, 2005.

Taniwaki *et al.*, Int J Oncol, 29(3):567-575, 2006.

Tassi *et al.*, *Cancer Res.*, 66(2):1191-1198, 2006.

Tassi *et al.*, *J. Biol. Chem.*, 276(43):40247-40253, 2001.

Thogersen *et al.*, Cancer Res, 61(16):6227-6233, 2001.

Thome, Nat Rev Immunol, 4(5):348-359, 2004.

Tomasini-Johansson *et al.*, Exp Cell Res, 214(1):303-312, 1994.

Torring *et al.*, Anticancer Res, 20(1A):91-95, 2000.

Toyoda *et al.*, Biochem J, 326 (Pt 1):69-75, 1997.

Traub *et al.*, Breast Cancer Res Treat, 99(2):185-191, 2006.

Troncone *et al.*, J Clin Pathol, 2006.

Tsai *et al.*, J Natl Cancer Inst, 1993. 85(11): p. 897-901.

Tseng *et al.*, Mol Pharmacol, 70(5):1534-1541, 2006.

Uemura *et al.*, Int J Mol Med, 18(2):365-373, 2006.

Uhm *et al.*, Clin Cancer Res, 5(6):1587-1594, 1999.

UK Appln. 8 803 000

UK Patent 1,529,202

Venkatasubbarao *et al.*, Anticancer Res, 20(1A):43-51, 2000.

Viard-Leveugle *et al.*, *J. Pathol.*, 201(2):268-277, 2003.

Visvader *et al.*, Proc Natl Acad Sci U S A, 98(25):14452-14457, 2001.

Vivanco and Sawyers, Nat Rev Cancer, 2(7):489-501, 2002.

Vogt *et al.*, Cell Cycle, 5(9):946-949, 2006.

Volinia *et al.*, Proc Natl Acad Sci U S A, 103(7):2257-2261, 2006.

Walker-Daniels *et al.*, Am J Pathol, 162(4):1037-1042, 2003.

Wang *et al.*, World J Gastroenterol, 11(3):336-339, 2005.

Weeraratna *et al.*, Cancer Cell, 1(3):279-288, 2002.

Weichert *et al.*, Int J Oncol, 23(3):633-639, 2003.

Weil *et al.*, Biotechniques, 2002. 33(6): p. 1244-8.

Weiss and Bohmann, Cell Cycle, 3(2):111-113, 2004.

Wheeler and Ridley, Exp Cell Res, 301(1):43-49, 2004.

Wikman *et al.*, Oncogene, 21(37):5804-5813, 2002.

Wilson *et al.*, J Biol Chem, 281(19):13548-13558, 2006.

Wooster and Weber, N Engl J Med, 348(23):2339-2347, 2003.

Woszczyk *et al.*, Med Sci Monit, 10(1):CR33-37, 2004.

Wu *et al.*, Breast Cancer Res Treat, 84(1):3-12, 2004b.

Wu *et al.*, Eur J Cancer, 38(14):1838-1848, 2002.

Wu *et al.*, Eur J Cancer, 42(4):557-565, 2006a.

Wu *et al.*, *Eur. J. Cancer,* 38(14):1838-1848, 2002.

Wu *et al.*, Gynecol Oncol, 102(1):15-21, 2006b.

Wu *et al.*, Int J Gynecol Cancer, 16(4):1668-1672, 2006b.

Wu *et al.*, Pathol Oncol Res, 10(1):26-33, 2004a.

Wuilleme-Toumi *et al.*, *Leukemia,* 19(7):1248-1252, 2005.

Xi *et al.*, *Clin. Cancer Res.*, 12(8):2484-2491, 2006a.

Xi *et al.*, *Clin. Chem.*, 52(3):520-523, 2006b.

Xia *et al.*, Cancer Res, 61(14):5644-5651, 2001b.

Xia *et al.*, Cancer, 91(8):1429-1436, 2001a.

Xia *et al.*, Urology, 59(5):774-778, 2002.

Xie *et al.*, BMC Cancer, 6:77, 2006.

Xu *et al.*, *Curr. Biol.*, 13(9):790-795, 2003.

Yamagata *et al.*, Cancer Res, 65(1):157-165, 2005.

Yang *et al.*, Cancer Cell, 9(6):445-457, 2006.

Yang *et al.*, *Cancer Res.,* 65(19):8887-8895, 2005.

Yang *et al.*, J Androl, 22(3):471-480, 2001.

Yao *et al.*, Oncogene, 25(16):2285-2296, 2006.

Yoshioka *et al.*, Proc Natl Acad Sci U S A, 100(12):7247-7252, 2003.

Yu *et al.*, Nat Genet, 37(3):265-274, 2005.

Zangemeister-Wittke and Huwiler, *Cancer Biol. Ther.*, 5(10):1355-1356, 2006.

Zeng *et al.*, Cancer Res, 62(12):3538-3543, 2002.

Zhang *et al.*, *Oncogene,* 23(12):2241-2249, 2004.

Zhang *et al.*, Oncogene, 25(45):6101-6112, 2006.

Zhao *et al.*, *Mol. Cancer Res.*, 1(3):195-206, 2003.

Zhu *et al.*, Biochem Biophys Res Commun, 273(3):1019-1024, 2000.

Zhu *et al.*, Cell, 94(6):703-714, 1998.

CLAIMS

1. A method of modulating gene expression in a cell comprising administering to the cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 nucleic acid sequence in an amount sufficient to modulate the expression of one or more genes identified in Table 1, 3, or 4, wherein

(a) miR-15 modulated genes are selected from Table 1A, 3A, or 4A;

(b) miR-26 modulated genes are selected from Table 1B, 3B, or 4B;

(c) miR-31 modulated genes are selected from Table 1C, or 3C;

(d) miR-145 modulated genes are selected from Table 1D, or 3D;

(e) miR-147 modulated genes are selected from Table 1E, 3E, or 4C;

(f) miR-188 modulated genes are selected from Table 1F, 3F, or 4D;

(g) miR-215 modulated genes are selected from Table 1G, 3G, or 4E;

(h) miR-216 modulated genes are selected from Table 1H, 3H, or 4F;

(i) miR-331 modulated genes are selected from Table 1I, 3I, or 4G; and

(j) miR-292 modulated genes are selected from Table 1J, 3J, or 4H.

2. The method of claim 1, wherein the cell is in a subject having, suspected of having, or at risk of developing a metabolic, an immunologic, an infectious, a cardiovascular, a digestive, an endocrine, an ocular, a genitourinary, a blood, a musculoskeletal, a nervous system, a congenital, a respiratory, a skin, or a cancerous disease or condition.

3. The method of claim 2, wherein the infectious disease or condition is a parasitic, bacterial, viral, or fungal infection.

4. The method of claim 2, wherein the cancerous condition is one or more of acute lymphoblastic leukemia; acute myeloid leukemia; anaplastic large cell lymphoma;

angiosarcoma; astrocytoma; B-cell lymphoma; bladder carcinoma; breast carcinoma; Burkitt's lymphoma; carcinoma of the head and neck; cervical carcinoma; chronic lymphoblastic leukemia; chronic myeloid leukemia; colorectal carcinoma; endometrial carcinoma; esophageal carcinoma; esophageal squamous cell carcinoma; Ewing's sarcoma; fibrosarcoma; gastric carcinoma; gastrinoma; glioblastoma; glioma; hepatoblastoma; hepatocellular carcinoma; ; high-grade non-Hodgkin lymphoma; high-risk myelodysplastic syndrome; Hodgkin lymphoma; Kaposi's sarcoma; laryngeal squamous cell carcinoma; larynx carcinoma; leiomyosarcoma; leukemia; lipoma; liposarcoma; lung carcinoma; mantle cell lymphoma; medulloblastoma; melanoma; mesothelioma; mucosa-associated lymphoid tissue B-cell lymphoma; multiple myeloma; myeloid leukemia; myxofibrosarcoma; nasopharyngeal carcinoma; neuroblastoma; neurofibroma; non-Hodgkin lymphoma; non-small cell lung carcinoma; osteosarcoma; ovarian carcinoma; pancreatic carcinoma; pheochromocytoma; prostate carcinoma; renal cell carcinoma; retinoblastoma; rhabdomyosarcoma; salivary gland tumor; schwannoma; small cell lung cancer; squamous cell carcinoma of the head and neck; testicular tumor; thyroid carcinoma; urothelial carcinoma; or Wilm's tumor wherein the modulation of one or more gene is sufficient for a therapeutic response.

5. The method of claim 1, wherein the expression of a gene is down-regulated.

6. The method of claim 1, wherein the cell is an epithelial, an endothelial, a mesothelial, a stromal, or a mucosal cell.

7. The method of claim 1, wherein the cell is a brain, a glial, a neuronal, a blood, a cervical, an endometrial, a meninges, an esophageal, a lung, a cardiovascular, a liver, a lymphoid, a breast, a bone, a connective tissue, a retinal, a thyroid, a glandular, an adrenal, a pancreatic, a stomach, an a intestinal, a kidney, a bladder, a colon, a prostate, a uterine, an ovarian, a cervical, a testicular, a splenic, a skin, a fat, a smooth muscle, a cardiac muscle, or a striated muscle cell.

8. The method of claim 1, wherein the cell is a cancer cell.

9. The method of claim 8, wherein the cancer cell is a neuronal, glial, lung, liver, brain, breast, bladder, blood, cardiovascular, leukemic, glandular, lymphoid, adrenal, colon, endometrial, epithelial, intestinal, meninges, mesothelial, stomach, skin, ovarian, uterine,

testicular, splenic, fat, bone, cervical, esophageal, pancreatic, prostate, kidney, retinal, connective tissue, smooth muscle, cardiac muscle, striated muscle, or thyroid cell.

10. The method of claim 1, wherein the isolated miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 nucleic acid is a recombinant nucleic acid.

11. The method of claim 10, wherein the recombinant nucleic acid is RNA.

12. The method of claim 10, wherein the recombinant nucleic acid is DNA.

13. The method of claim 12, wherein the recombinant nucleic acid comprises a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 expression cassette.

14. The method of claim 13, wherein the expression cassette is comprised in a viral vector, or plasmid DNA vector.

15. The method of claim 14, wherein the viral vector is administered at a dose of $1x10^5$ to $1x10^{14}$ viral particles per dose or the plasmid DNA vector is administered at a dose of 100 mg per patient to 4000 mg per patient.

16. The method of claim 1, wherein the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 nucleic acid is a synthetic nucleic acid.

17. The method of claim 16, wherein the nucleic acid is administered at a dose of 0.01 mg/kg of body weight to 10 mg/kg of body weight.

18. The method of claim 1, wherein the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 is a human miR.

19. The method of claim 1, wherein the nucleic acid is administered enterally or parenterally.

20. The method of claim 19, wherein enteral administration is orally.

21. The method of claim 19, wherein parenteral administration is intravascular, intracranial, intrapleural, intratumoral, intraperitoneal, intramuscular, intralymphatic, intraglandular, subcutaneous, topical, intrabronchial, intratracheal, intranasal, inhaled, or instilled.

22. The method of claim 1, wherein the nucleic acid is comprised in a pharmaceutical formulation.

23. The method of claim 22, wherein the pharmaceutical formulation is a lipid composition.

24. A method of modulating a cellular pathway or a physiologic pathway comprising administering to a cell an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 nucleic acid sequence in an amount sufficient to modulate the cellular pathway or physiologic pathway that includes one or more genes identified or gene products related to one or more genes identified in Table 1, 3, or 4, wherein

(a) miR-15 modulated genes are selected from Table 1A, 3A, or 4A;

(b) miR-26 modulated genes are selected from Table 1B, 3B, or 4B;

(c) miR-31 modulated genes are selected from Table 1C, or 3C;

(d) miR-145 modulated genes are selected from Table 1D, or 3D;

(e) miR-147 modulated genes are selected from Table 1E, 3E, or 4C;

(f) miR-188 modulated genes are selected from Table 1F, 3F, or 4D;

(g) miR-215 modulated genes are selected from Table 1G, 3G, or 4E;

(h) miR-216 modulated genes are selected from Table 1H, 3H, or 4F;

(i) miR-331 modulated genes are selected from Table 1I, 3I, or 4G; and

(j) miR-292 modulated genes are selected from Table 1J, 3J, or 4H.

25. The method of claim 24, further comprising administering 2, 3, 4, 5, 6, or more miRNAs.

26. The method claim 25 wherein the miRNAs are comprised in a single composition.

27. The method of 25, wherein at least two cellular pathways or physiologic pathways are modulated.

28. The method of claim 25, wherein at least one gene is modulated by multiple miRNAs.

29. The method of claim 24, wherein the expression of a gene or a gene product is down-regulated.

30. The method of claim 24, wherein the expression of a gene or a gene product is down-regulated.

31. The method of claim 24, wherein the cell is a cancer cell.

32. The method of claim 31, wherein viability of the cell is reduced, proliferation of the cell is reduced, metastasis of the cell is reduced, or the cell's sensitivity to therapy is increased.

33. The method of claim 31, wherein the cancer cell is a neuronal, glial, lung, liver, brain, breast, bladder, blood, cardiovascular, leukemic, glandular, lymphoid, adrenal, colon, endometrial, epithelial, intestinal, meninges, mesothelial, stomach, skin, ovarian, uterine, testicular, splenic, fat, bone, cervical, esophageal, pancreatic, prostate, kidney, retinal, connective tissue, smooth muscle, cardiac muscle, striated muscle, or thyroid cell.

34. The method of claim 24, wherein the isolated miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or miR-331, miR-292 nucleic acid is a recombinant nucleic acid.

35. The method of claim 34, wherein the recombinant nucleic acid is DNA.

36. The method of claim 35, wherein the recombinant nucleic acid is a viral vector or a plasmid DNA. vector.

37. The method of claim 24, wherein the nucleic acid is RNA.

38. The method of claim 24, wherein the miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, or miR-331, miR-292 nucleic acid is a synthetic nucleic acid.

39. The method of claim 34, wherein the recombinant nucleic acid is a synthetic nucleic acid.

40. A method of treating a patient diagnosed with or suspected of having or suspected of developing a pathological condition or disease related to a gene modulated by a miRNA comprising the steps of:

(a) administering to the patient an amount of an isolated nucleic acid comprising a miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 nucleic acid sequence in an amount sufficient to modulate a cellular pathway or a physiologic pathway; and

(b) administering a second therapy, wherein the modulation of the cellular pathway or physiologic pathway sensitizes the patient to the second therapy.

41. The method of claim 40, wherein one or more cellular pathway or physiologic pathway includes one or more genes identified in Table 1, 3, or 4, wherein

(a) miR-15 modulated genes are selected from Table 1A, 3A, or 4A;

(b) miR-26 modulated genes are selected from Table 1B, 3B, or 4B;

(c) miR-31 modulated genes are selected from Table 1C, or 3C;

(d) miR-145 modulated genes are selected from Table 1D, or 3D;

(e) miR-147 modulated genes are selected from Table 1E, 3E, or 4C;

(f) miR-188 modulated genes are selected from Table 1F, 3F, or 4D;

(g) miR-215 modulated genes are selected from Table 1G, 3G, or 4E;

(h) miR-216 modulated genes are selected from Table 1H, 3H, or 4F;

(i) miR-331 modulated genes are selected from Table 1I, 3I, or 4G; and

(j) miR-292 modulated genes are selected from Table 1J, 3J, or 4H.

42. A method of selecting a miRNA to be administered to a subject with, suspected of having, or having a propensity for developing a pathological condition or disease comprising:

(a) determining an expression profile of one or more genes selected from Table 1, 3, or 4;
(b) assessing the sensitivity of the subject to miRNA therapy based on the expression profile; and
(c) selecting one or more miRNA based on the assessed sensitivity.

43. The method of claim 42, further comprising treating the subject with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more miRNAs.

44. The method of claim 43, wherein each miRNA is administered individually or in one or more combinations.

45. The method of claim 44, wherein the miRNAs are in a single composition.

46. A method of assessing a cell, tissue, or subject comprising assessing expression of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 in combination with assessing expression of one or more gene from Table 1, 3, or 4, in at least one sample.

47. A method of assessing miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 status in a sample comprising the steps of:

(a) assessing expression of one or more genes from Table 1, 3, or 4 in a sample; and
(b) determining miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 status based on the level of miR-15, miR-26, miR-31, miR-145, miR-147, miR-188, miR-215, miR-216, miR-331, or miR-292 expression in the sample.

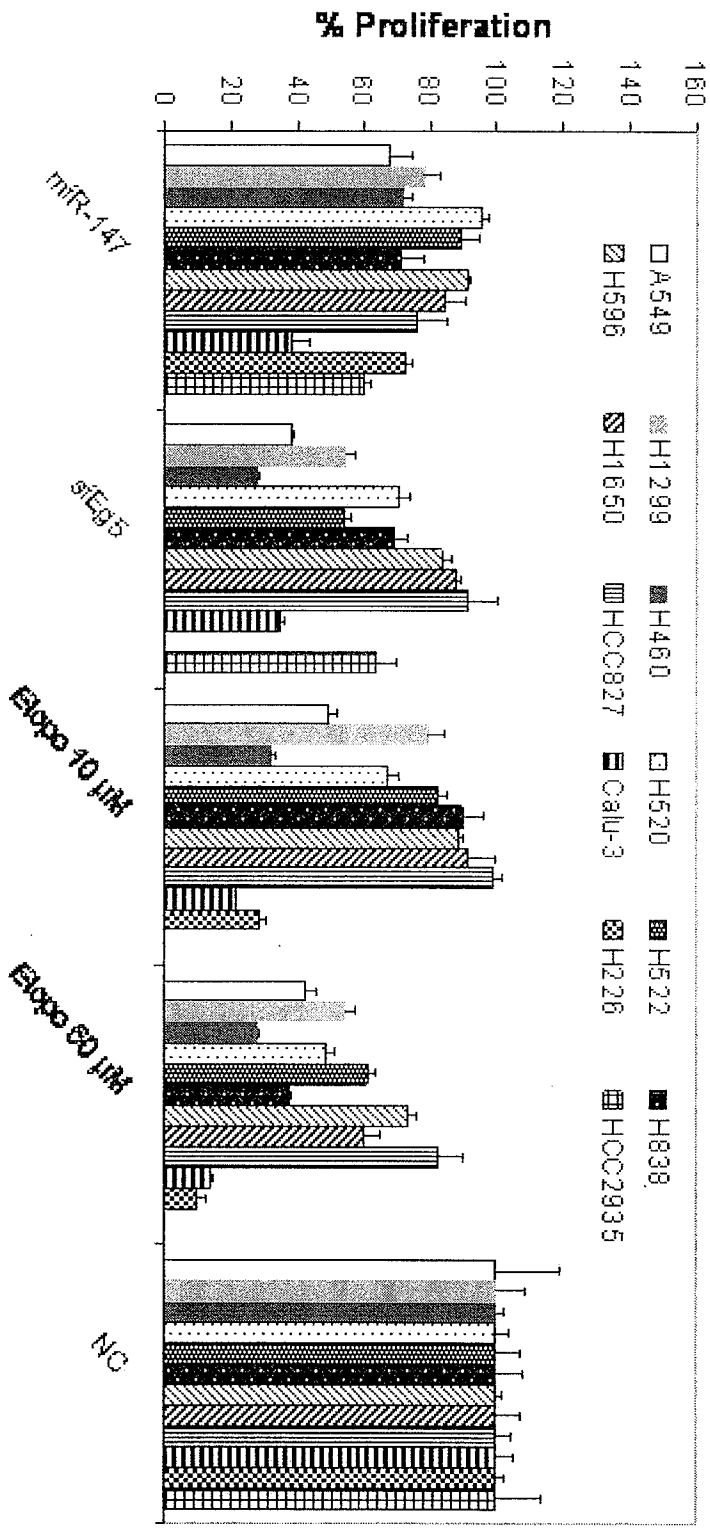
% Proliferation
0
20
40
60
80
100
120
140
160
miR-147
siEg5
Etopo 10 μM
Etopo 50 μM
NC
A549
H1299
H460
H520
H522
H838
H596
H1650
HCC827
Calu-3
H226
HCC2935

FIG. 1

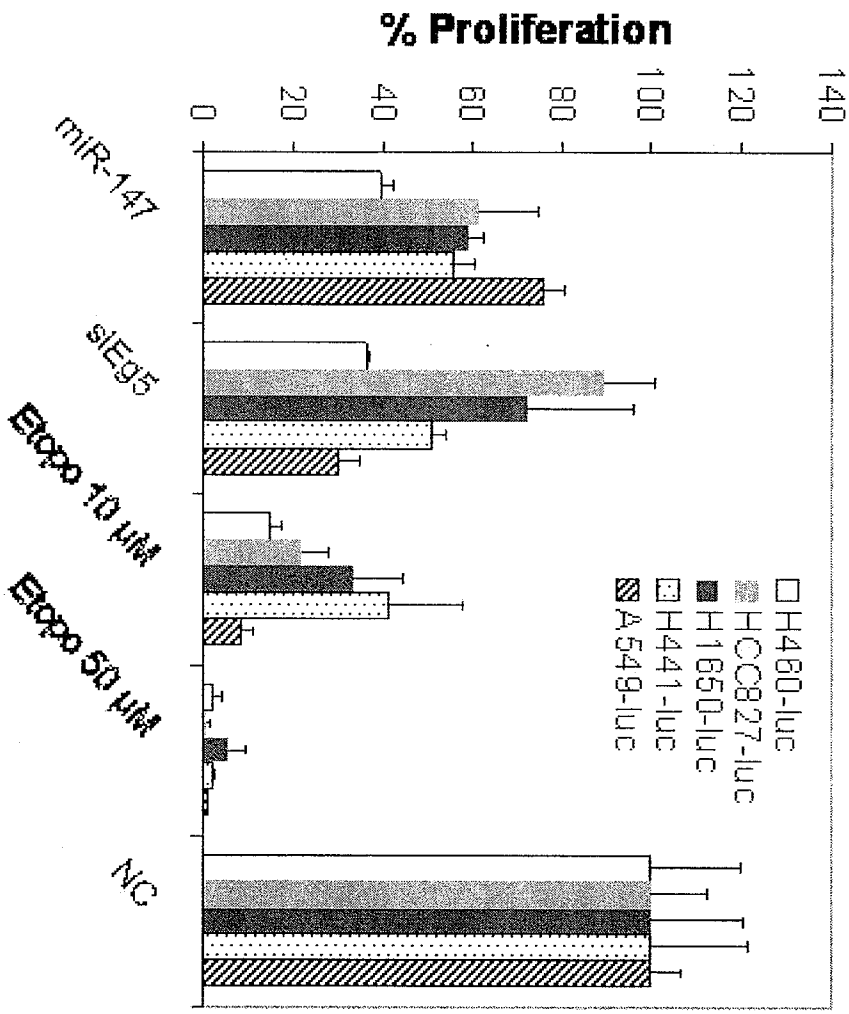
% Proliferation
0
20
40
60
80
100
120
140
miR-147
siEg5
Etopo 10 μM
Etopo 50 μM
NC
H460-luc
HCC827-luc
H1650-luc
H441-luc
A549-luc

FIG. 2

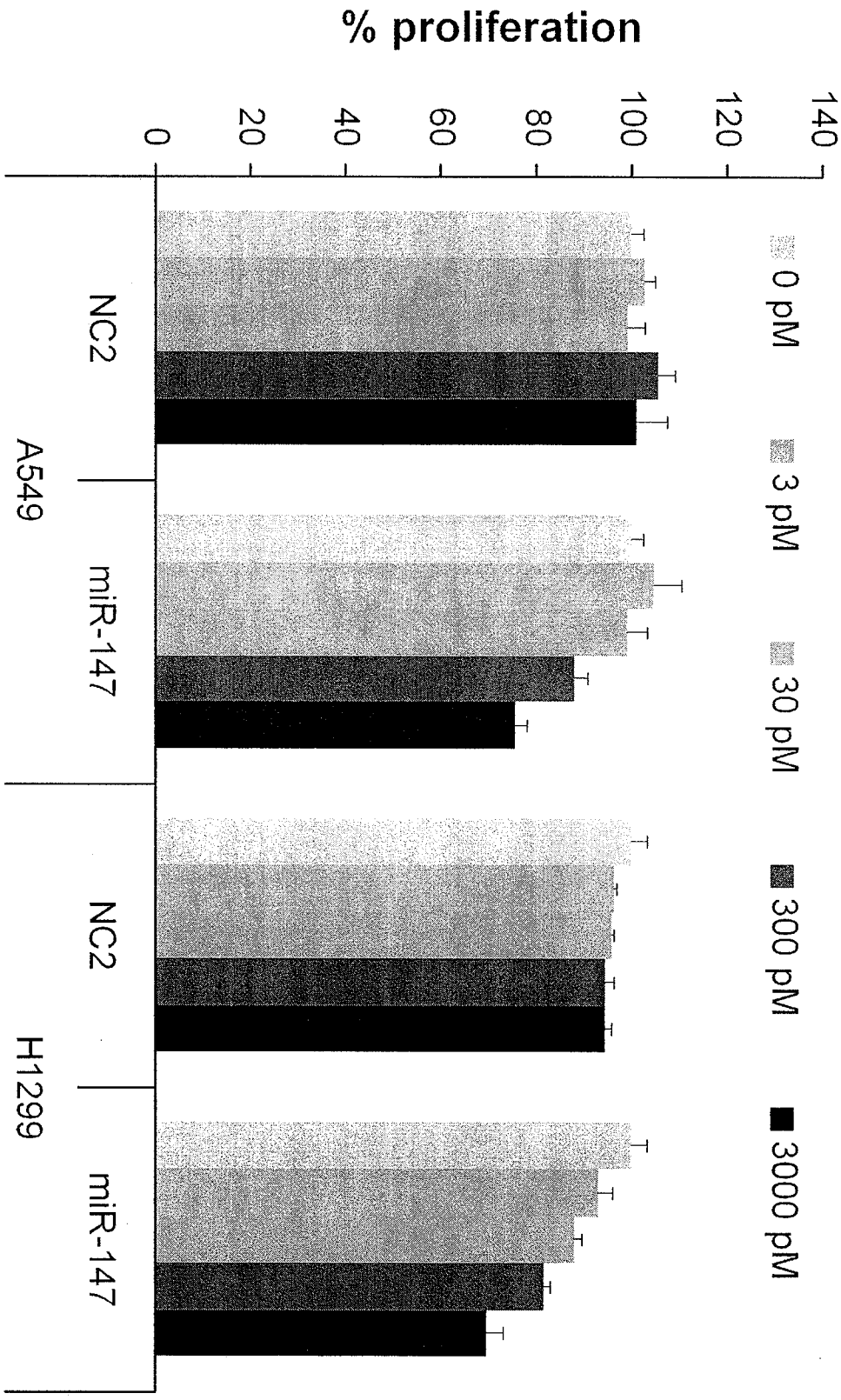
% proliferation
0
20
40
60
80
100
120
140
0 pM
3 pM
30 pM
300 pM
3000 pM
NC2
miR-147
NC2
miR-147
A549
H1299

FIG. 3

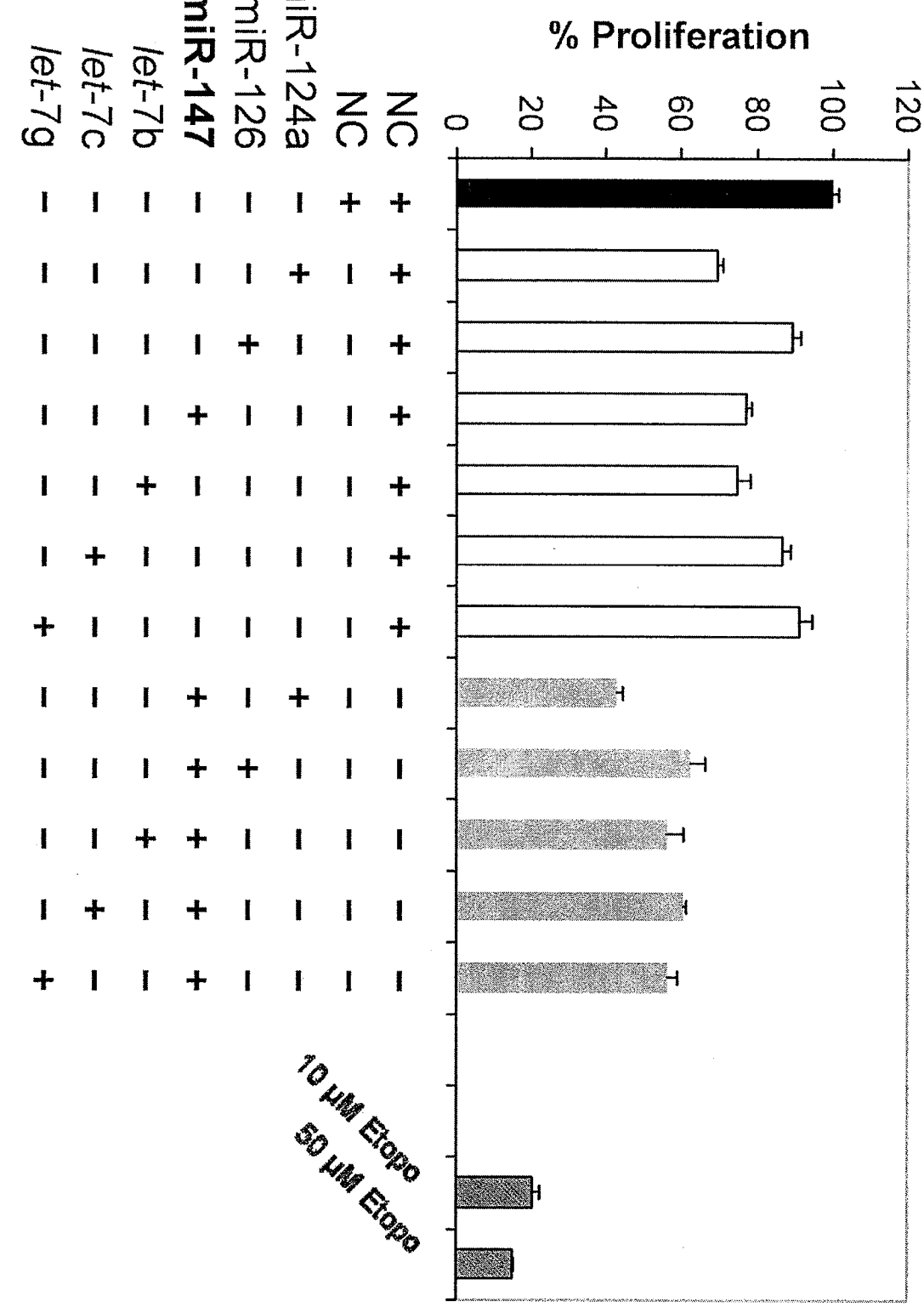
% Proliferation
0
20
40
60
80
100
120
NC
NC
miR-124a
miR-126
miR-147
let-7b
let-7c
let-7g
10 μM Etopo
50 μM Etopo

FIG. 4

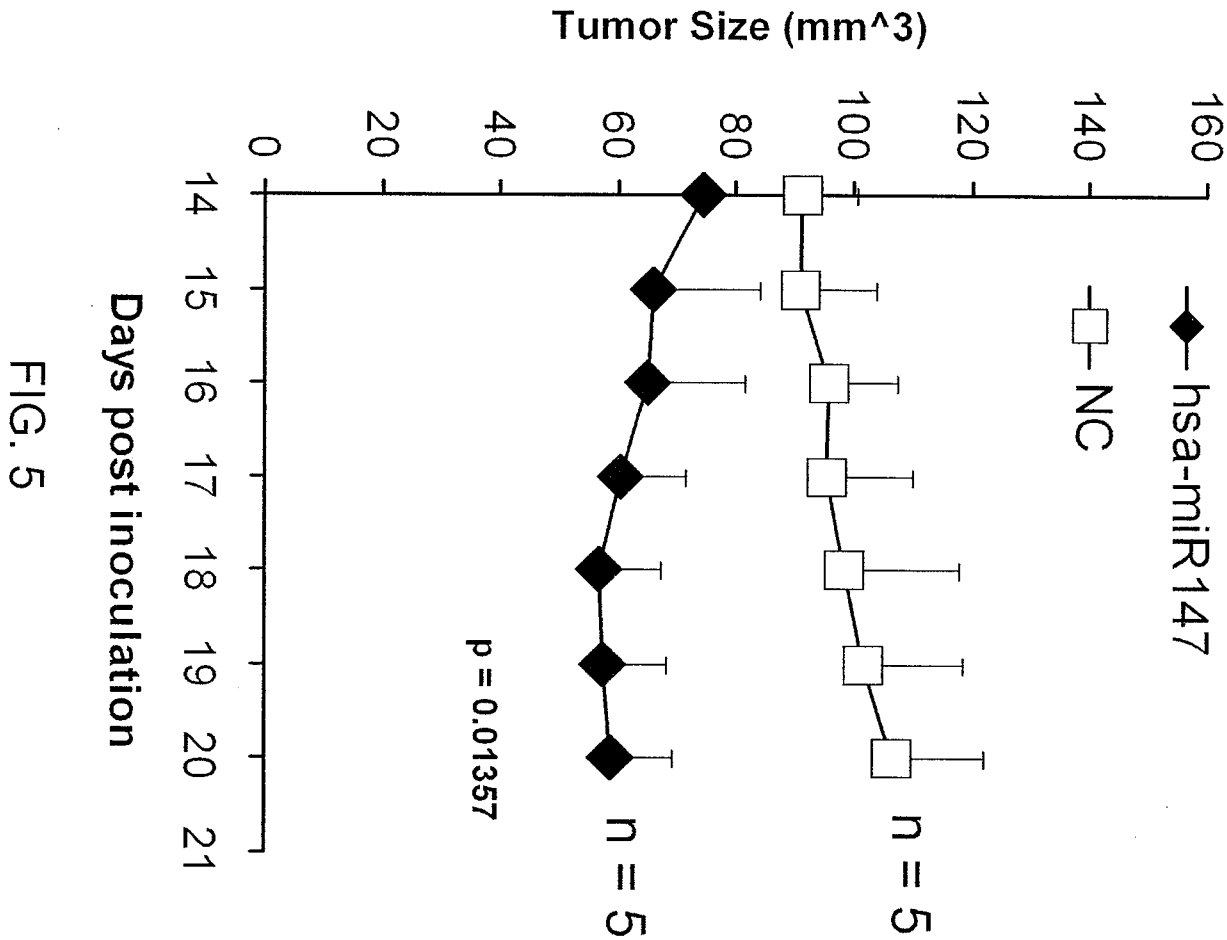
Tumor Size (mm^3)
0
20
40
60
80
100
120
140
160
14
15
16
17
18
19
20
21
Days post inoculation
hsa-miR147
NC
n = 5
n = 5
p = 0.01357

FIG. 5