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- (71) Applicant: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; Technology Ventures, 3400 N. Charles Street, Clark 106, Baltimore, MD 21218 (US).
- (72) Inventors: **LUPOLD, Shawn, E.**; 2302 Mount Hebron Dr., Ellicott City, MD 21042 (US). **HATANO, Koji**; 6705 Maple Leaf Ct. 102, Baltimore, MD 21209 (US). **KUMAR, Binod**; 302 Stevenson Lane, Apt. C5, Baltimore, MD 21204 (US). **DEWEESE, Theodore, L.**; 610 East Seminary Avenue, Towson, MD 21286 (US).
- (74) Agents: **CORLESS, Peter, F.** et al.; Mintz Levin Cohn Ferris Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

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(54) Title: SENSITIZING AGENT FOR CANCER CHEMOTHERAPY AND RADIATION THERAPY AND USES THEREOF

FIG. 1A

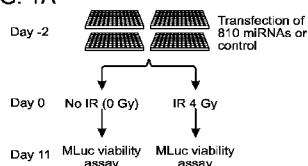


FIG. 1C

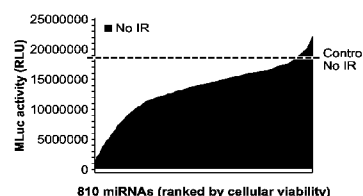


FIG. 1B

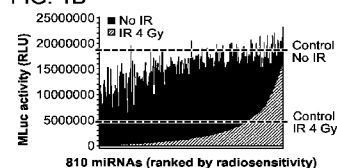
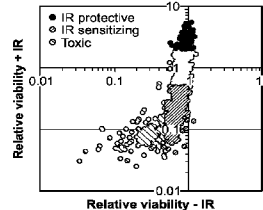


FIG. 1D



(57) Abstract: The present disclosure provides compositions and methods whereby specific microRNA (miRNA) is utilized as a means to sensitize cancer cells to radiation or chemotherapy.

SENSITIZING AGENT FOR CANCER CHEMOTHERAPY AND RADIATION THERAPY AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No: 62/135,429, filed March 19, 2015, which is incorporated herein by reference in its entirety.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with U.S. Government support under Grant Number R01CA143299 and P50CA058236 from the National Cancer Institute. The Government has certain rights in the invention.

FIELD OF THE DISCLOSURE

[0003] The present invention relates to cancer therapeutics and uses thereof.

BACKGROUND OF THE DISCLOSURE

[0004] MicroRNAs (miRNAs) have been implicated in DNA repair pathways through transcriptional responses to DNA damaging agents and through the predicted regulation of DNA repair pathway genes. Ionizing radiation (IR) is a useful modality to treat multiple types of cancers. The primary cellular injury associated with IR is DNA damage; in particular DNA double strand breaks (DSBs). Activated DNA damage response (DDR) pathways control downstream effectors which can determine cellular fates such as DNA repair, cell cycle arrest or apoptosis. Tumor cells often present radiation protective phenotypes which can lead to IR treatment failure. A number of mechanisms account for this resistance including tumor microenvironment and altered cellular gene expression of DDR pathway components. As such, a better understanding of DDR pathways in cancer is needed for improved treatment design and efficacy.

SUMMARY OF THE DISCLOSURE

[0005] Prior to the invention described herein, methods for sensitizing cancer cells utilized pharmaceutical agents or RNA interference (RNAi) agents such as siRNAs or shRNAs. The present disclosure provides compositions and methods whereby specific microRNA

(miRNA) is utilized as a means to sensitize cancer cells to radiation or chemotherapy. Described herein is the ability of miRNA, including miR-890-5p and miR-744-3p, to enhance the anti-cancer effect of radiation therapy and to inhibit DNA repair processes following radiation therapy.

[0006] The present invention provides a method of improving a cancer therapeutic response to radiation therapy or chemotherapy in a subject, the method comprising administering to a subject an effective amount of miR-890-5p or an agent that enhances the expression of miR-890-5p or an agent that mimics the effects of miR-890-5p either prior to or in conjunction with a radiation therapy or a chemotherapy. The microRNA miR-890-5p inhibits DNA repair processes by suppressing the expression of several targets (including MAD2L2 (which encodes mitotic spindle assembly checkpoint protein MAD2B) and WEE1). This can be achieved through the administration of miR-890-5p. Alternate methods of activating endogenous miR-890-5p or mimicking miR-890-5p are also considered.

[0007] The present invention provides a method of improving a cancer therapeutic response to radiation therapy or chemotherapy in a subject, the method comprising administering to a subject an effective amount of miR-744-3p or an agent that enhances the expression of miR-744-3p or an agent that mimics the effects of miR-744-3p either prior to or in conjunction with a radiation therapy or chemotherapy. The present disclosure provides a method to increase the sensitivity of a cancer cell to radiation therapy or chemotherapy through the administration of microRNA miR-744-3p. The microRNA, miR-744-3p, inhibits DNA repair processes by suppressing the expression of several targets (including MAD2L2 and WEE1). This can be achieved through the administration of miR-744-3p. Alternate methods of activating endogenous miR-744-3p or mimicking miR-744-3p are also considered.

[0008] Described herein is a composition for increasing sensitization to ionizing radiation (IR) comprising an miRNA; miRNA mimetic, activator of miRNA, or mixture thereof.

[0009] In certain examples, the miRNA is miR-744. For example, the miRNA is miR-744-3p or miR-744-5p. miR-744-3p comprises SEQ ID NO: 734. In certain examples, the miRNA comprises miR-890. For example, the miRNA comprises miR-890-5p or miR-890-3p. miR-890-5p comprises SEQ ID NO: 764. The activator of miRNA activates endogenous miR-890-5p or miR-744-3p when administered to a patient. The miRNA mimetic mimics miR-890-5p or miR-744-3p.

[0010] A composition described herein can further comprise a chemotherapeutic agent. Suitable chemotherapeutic agents are described herein.

[0011] The composition is administered 1-5 days prior to treatment with IR. For example, the composition is administered 1 day, 2 days, 3 days, 4 days, or 5 days prior to treatment with IR. Alternatively, the composition is administered 1-5 days after treatment with IR. For example, the composition is administered 1 day, 2 days, 3 days, 4 days, or 5 days after treatment with IR.

[0012] In one aspect, the dose of IR comprises between 0 Gy and 30 Gy in a single fraction of externally applied radiation. Alternatively, the dose of IR comprises between 0 Gy and 20 Gy per fraction in multiple fractions by externally applied radiation. In yet another aspect, the dose of IR comprises low dose rate brachytherapy dosing of 0 – 2 Gy/minute. Optionally, the dose of IR comprises high dose rate brachytherapy dosing of 2 – 20 Gy/minute.

[0013] Also described herein is a method of increasing sensitivity to ionizing radiation (IR) therapy or chemotherapy in a patient in need thereof. The method includes administering to the patient in need thereof a composition comprising an miRNA, miRNA mimetic, activator of miRNA, or mixture thereof. For example, the miRNA is miR-744, e.g., miR-744-3p or miR-744-5p. In one aspect, miR-744-3p comprises SEQ ID NO: 734. Alternatively, the miRNA is miR-890, e.g., miR-890-5p or miR-890-3p. In one aspect, miR-890-5p comprises SEQ ID NO: 764.

[0014] In methods described herein, the composition is administered prior to IR treatment, e.g., 1-5 days prior to treatment with IR. Alternatively, the composition is administered after IR treatment, e.g., 1-5 days after treatment with IR. The dose of IR comprises between 0 Gy and 30 Gy in a single fraction of externally applied radiation. In another aspect, the dose of IR comprises between 0 Gy and 20 Gy per fraction in multiple fractions by externally applied radiation. Alternatively, the dose of IR comprises low dose rate brachytherapy dosing of 0 – 2 Gy/minute. Optionally, the dose of IR comprises high dose rate brachytherapy dosing of 2 – 20 Gy/minute.

[0015] In one aspect, the composition is co-administered with a chemotherapeutic agent. Suitable chemotherapeutic agents are described herein.

[0016] In methods described herein, the patient in need thereof is a patient with cancer or a tumor. Suitable cancers include skin cancer, brain cancer and other central nervous system cancers, head cancer, neck cancer, muscle/sarcoma cancer, bone cancer, lung cancer, esophagus cancer, stomach cancer, pancreas cancer, colon cancer, rectum cancer, uterus cancer, cervix cancer, vagina cancer, vulva cancer, penis cancer, breast cancer, kidney

cancer, prostate cancer, bladder cancer, or thyroid cancer. In some cases, the patient is a patient with glioblastoma.

[0017] Also provided are methods of increasing sensitivity to IR therapy or chemotherapy in a tumor cell. The method includes contacting the tumor cell with a composition comprising an miRNA, miRNA mimetic, activator of miRNA, or mixture thereof, thereby increasing sensitivity to IR therapy or chemotherapy.

[0018] As used herein “miRNAs” are small non-coding RNAs which post-transcriptionally regulate gene expression through interaction with the 3’ untranslated regions (3’UTRs) of mRNAs. Relatively conserved miRNA sequences with similar functions are referred to as “miRNA families”. For example, miR-890 is a member of the miR-743 family (e.g., those found online at mirbase.org/cgi-bin/mirna_summary.pl?fam=MIPF0000386). Furthermore, microRNAs have two functional sequences that are released from either side of a pre-miRNA hairpin structure (the -5p and -3p mature microRNAs). For example, miR-744 forms a hairpin structure of miR-744-5p and miR-744-3p (also referred to as miR-744 and miR-744* respectively). If miR-744 is expressed as a gene, it will produce both miR-744-5p and miR-744-3p. The -5p and -3p mature microRNAs are different sequences and often have different functions.

[0019] The “seed sequence” of the miRNA comprises nucleotides 2-8 at the 5’ end of the miRNA. The miRNA seed sequence is complementary to the target mRNA sequence. The remaining nucleotides of the miRNA is, in some cases, not perfectly complementary to the target mRNA. Thus, nucleotides not present in the seed sequence are not required for binding.

[0020] As used herein, the term “siRNA” refers to a double stranded stretch of RNA or modified RNA monomers. In a typical siRNA compound, the two strands usually have 19 nucleotides complementary to each other, thereby creating a double strand that is 19 nucleotides long and each strand having a 3’-end of two overhanging nucleotides. This is not a strict definition of siRNA, which may be slightly longer or shorter, and with or without overhangs. In siRNA, one strand is guiding and complementary to the target RNA (antisense strand), and the other strand (sense strand) has the same sequence as the target RNA and hence is complementary to the guide antisense strand. As used herein, the term “mRNA” means the presently known mRNA transcript(s) of a targeted gene, and any further transcripts, which may be identified.

[0021] As used herein the term “shRNA” means that a single strand RNA of 50 to 100 nucleotides forms a stem-loop structure in a cell, which contains a loop region of 5 to 30 nucleotides, and long complementary RNAs of 15 to 50 nucleotides at both sides of the loop region, which form a double-stranded stem by base pairing between the complementary RNAs; and additional 1 to 500 nucleotides included before and after each complementary strand forming the stem. shRNA is usually transcribed by RNA polymerase in a cell, and subsequently cleaved in the nucleus by Drosha, and the cleaved shRNA is exported from the nucleus to cytosol, and further cleaved in the cytosol by Dicer. Like siRNA, shRNA binds to the target mRNA in a sequence specific manner, thereby cleaving and destroying the target mRNA, and thus suppressing expression of the target mRNA.

[0022] Ionizing radiation may be quantified and expressed in terms of a gray (Gy). One gray is the absorption of one joule of energy, in the form of ionizing radiation, by one kilogram of matter. For X-rays and gamma rays, these are the same units as the sievert (Sv). To avoid any risk of confusion between the absorbed dose and the equivalent dose, one must use the corresponding special units, namely the gray instead of the joule per kilogram for absorbed dose and the sievert instead of the joule per kilogram for the dose equivalent. The gray measures the deposited energy of radiation. The biological effects vary by the type and energy of the radiation and the organism and tissues involved. The sievert attempts to account for these variations.

[0023] As used herein “cancer” may refer to any one of a cancerous cell proliferative disorder including, for example, cancers or tumors of the skin, brain and other central nervous system sites, head, neck, muscle/sarcoma, bone, lung, esophagus, stomach, pancreas, colon, rectum, uterus, cervix, vagina, vulva, penis, breast, kidney, prostate, bladder, and thyroid.

[0024] As used herein, “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder.

[0025] A composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, can also be used to prevent a disease, condition or disorder. As used herein, “preventing” or “prevent” describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[0026] The terms "isolated," "purified," or "biologically pure" refer to material that is free to varying degrees from components which normally accompany it as found in its native state. "Isolate" denotes a degree of separation from original source or surroundings. "Purify" denotes a degree of separation that is higher than isolation.

[0027] A "purified" or "biologically pure" nucleic acid is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the nucleic acid or cause other adverse consequences. That is, a nucleic acid of this invention is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term "purified" can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example, phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified.

[0028] Similarly, by "substantially pure" is meant a nucleotide molecule that has been separated from the components that naturally accompany it. Typically, the nucleotides are substantially pure when they are at least 60%, 70%, 80%, 90%, 95%, or even 99%, by weight, free from the proteins and naturally-occurring organic molecules with they are naturally associated.

[0029] By "isolated nucleic acid" is meant a nucleic acid that is free of the genes which flank it in the naturally-occurring genome of the organism from which the nucleic acid is derived. The term covers, for example: (a) a DNA which is part of a naturally occurring genomic DNA molecule, but is not flanked by both of the nucleic acid sequences that flank that part of the molecule in the genome of the organism in which it naturally occurs; (b) a nucleic acid incorporated into a vector or into the genomic DNA of a prokaryote or eukaryote in a manner, such that the resulting molecule is not identical to any naturally occurring vector or genomic DNA; (c) a separate molecule such as a synthetic cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment; and (d) a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. Isolated nucleic acid molecules according to the present invention further include molecules produced synthetically, as well as any nucleic acids that have been altered chemically and/or that have modified backbones. For example, the isolated nucleic acid is a

purified cDNA or RNA polynucleotide. Isolated nucleic acid molecules also include messenger ribonucleic acid (mRNA) molecules.

[0030] By “reduces” is meant a negative alteration of at least 5%, 10%, 25%, 50%, 75%, or 100%.

[0031] By “substantially identical” is meant a nucleic acid molecule exhibiting at least 50% identity to a reference nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, more preferably 80% or 85%, and more preferably 90%, 95% or even 99% identical at the nucleic acid to the sequence used for comparison.

[0032] Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence.

[0033] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 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, or 50.

[0034] Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms “a”, “an”, and “the” are understood to be singular or plural.

[0035] Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

[0036] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

[0037] The transitional term “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. By contrast, the transitional phrase “consisting of” excludes any element, step, or ingredient not specified in the claim. The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention.

[0038] Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All published foreign patents and patent applications cited herein are incorporated herein by reference. Genbank and NCBI submissions indicated by accession number cited herein are incorporated herein by reference. All other published references, documents, manuscripts and scientific literature cited herein are incorporated herein by reference. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] **Figs. 1A-D** show high-throughput functional screening for miRNAs which modulate prostate cancer viability and radiosensitivity. **Fig. 1A** is a schematic representation of the high-throughput miRNA functional screening. **Fig. 1B** shows the average viable cell density (represented by MLuc activity) of irradiated (red) and non-irradiated (blue) LNCaP-MLuc cells on day 11. The data is organized as a waterfall plot for each miRNA ranked by sensitivity to IR. Average cell response to control miRNAs, with and without IR, are represented by dashed lines. RLU; Relative Light Units. **Fig. 1C** shows the average LNCaP-MLuc viable cell density (represented by MLuc activity) after treatment with 810 different miRNAs, in the absence of IR. Results are a waterfall plot ranked by viable cell density. Average signal with a control miRNA is represented as a dashed line. **Fig. 1D** shows four different categories of miRNA responses based on cell viability and

radiation sensitivity modulated by 810 miRNAs. The MLuc activity for each miRNA was normalized to control miRNAs and quantified as relative cell viability with or without IR.

[0040] **Figs. 2A -B** demonstrate candidate radiation sensitizing miRNA validation by MLuc assay and clonogenic survival assay. **Fig. 2A** shows LNCaP-MLuc or PC3-MLuc cell radiosensitivity with candidate miRNAs, negative control miRNA (cel-miR-239b) or positive control DNAPK siRNA (siDNAPK). The % cell viability (mean $\pm$ S.E., n=3) following IR (4Gy) is presented by the ratio of MLuc activity for irradiated cells to non-irradiated cells for each miRNA on day 11. Control miRNA is noted by the dash line. *, $P < 0.05$. **Fig. 2B** plots a clonogenic survival assay of DU145 cells transfected with candidate radiation sensitizing miRNAs or control miRNA. The surviving fraction is reported (mean $\pm$ S.D., n=3) following the indicated doses of IR. *, $P < 0.05$. DMF. Dose Modifying Factor.

[0041] **Figs. 3A-D** demonstrate DSB repair delay by radiation sensitizing miRNAs. **Fig. 3A** is a series of images showing immunofluorescent staining of γ -H2AX (green) in DU145 cells transfected with control, miR-890-5p or miR-744-3p miRNAs in untreated (0 Gy) or 1 and 8 h after IR (4 Gy) treatment. Nuclei were stained with DAPI (blue). **Fig. 3B** is a graphic quantification of γ -H2AX foci. The percentage of cells containing >10 γ -H2AX foci (mean $\pm$ S.E., $n \geq 3$) is reported. *, $P < 0.05$. **Fig. 3C** is an image of a comet assay in DU145 cells transfected with control, miR-890-5p or miR-744-3p miRNAs and untreated (0 Gy) or 4 h after IR (4 Gy) treatment. **Fig. 3D** is a graphic quantification of the average tail moment (mean $\pm$ S.E., $n \geq 50$) is reported. *, $P < 0.05$.

[0042] **Figs. 4A-C** demonstrate that miR-890-5p and miR-744-3p directly target MAD2L2 and RAD23B. **Fig. 4A** is an image of western blot assays of four prostate cancer cell lines for MAD2L2 (left) and RAD23B (right) 48 h after miRNA mimetic transfection. **Fig. 4B** is a graph representation of the MAD2L2 and RAD23B 3'UTR miRNA binding sites. Mutated (Mut) MAD2L2 and RAD23B seed sequences are indicated (red). **Fig. 4C** is a graphic representation of Luciferase activities following transfection with indicated 3'UTR reporters and miRNA mimetics. Relative luciferase activity (mean $\pm$ S.E., n=4) is normalized to control miRNA for each reporter. *, $P < 0.05$ relative to control miRNAs.

[0043] **Figs. 5A-D** show that multiple DDR pathway genes targeted by radiation sensitizing miRNAs. **Figs. 5A-B** are images of western blot analyses of (**Fig. 5A**) MAD2L2, WEE1, XPC, and KU80 in and (**Fig. 5B**) RAD23B, XLF and MCL1 48 h after LNCaP transfection with indicated miRNA mimetics. Asterisk represents a nonspecific band. **Figs. 5C-D** are

graphs of quantified percent protein knock-down (mean $\pm$ S.E., n=3) by (**Fig. 5C**) miR-890-5p and (**Fig. 5D**) miR-744-3p, relative to control (from three separate experiments).

[0044] **Figs. 6A-C** show that miR-890-5p targets multiple proteins to enhance IR therapeutic effect. **Fig. 6A** is an image of a western blot 48 h after transfection showing MAD2L2 knock-down by siRNA (siMAD2L2), miR-890, or combined siRNA and miR-890-5p in LNCaP cells (10 nM). **Fig. 6B** is a graphic representation of IR sensitization potency of siMAD2L2 and/or miR-890-5p (0.08-10 nM) in LNCaP-MLuc cells. Relative cell viability (mean $\pm$ S.E., n=12) is presented as the MLuc activity after IR (4Gy), as normalized by control miRNA. *, $P < 0.05$. **Fig. 6C** is a graph of the calculated IC_{50} value of each treatment group, based on relative cell viability after IR.

[0045] **Figs. 7A-B** show that miR-890-5p mimetic injection enhances IR therapy of established prostate tumors. **Fig. 7A** is a graph of tumor volume for established subcutaneous DU145 tumors (n=3-5 per group) that were directly injected with PBS or liposomal-loaded miRNA mimetics. Two day after injection (day 0) tumors were irradiated with 6 Gy or no IR. miR-890-5p significantly reduced tumor volume in irradiated groups when compared to controls. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$; 2-way ANOVA. Mean $\pm$ SEM. **Fig. 7B** is a graph showing the extension of tumor quadrupling for DU145 tumor model. Events (animals whose tumor volume was not yet 4-fold the size at injection) were plotted by Kaplan-Meier curve. miR-890-5p significantly extended time to tumor quadrupling in irradiated groups when compared to controls. $P < 0.01$; log-rank (Mantel-Cox) test.

[0046] **Figs. 8A-B** demonstrate the radiation sensitization efficacy of DNAPK siRNA in LNCaP-MLuc cells. DNAPK siRNA was used as a positive control for each 96 well LNCaP-MLuc plate of the high throughput miRNA radiosensitivity screening. Two days before IR, each plate contained wells which were transfected with either DNAPK siRNA or control. On day 0, plates were irradiated at 4 Gy or remained untreated. On day 11, the cell viability and radiation sensitivity were determined by the MLuc viability assay (RLU; Relative Light Units). **Fig. 8A** is a graph of the MLuc activity of each group (mean $\pm$ S.E., n=132). **Fig. 8B** is a graph of the relative cell viability after IR (mean $\pm$ S.E., n=132) is presented as the MLuc activity of irradiated cells normalized by that of untreated cells. *, $P < 0.05$.

[0047] **Figs. 9A-B demonstrate the reproducibility of the high-throughput functional miRNA screening.** The high-throughput miRNA screening for cell growth and IR response was performed with duplicate wells for each miRNA and treatment condition, forming Group 1 and Group 2. The correlation of viable cell number for each miRNA, as measured by

relative MLuc activity normalized by control in Group 1 and Group 2, is plotted for the (**Fig. 9A**) non-irradiated and (**Fig. 9B**) IR samples. The linear correlation coefficient (R^2) between the two groups is noted.

[0048] **Fig. 10** is a graph showing radiosensitization by miRNAs from individual miRNA families. The radiation sensitization of LNCaP-MLuc cells from high-throughput miRNA screening for the individual miRNA families miR-15/16, miR-1/133, and miR-106b. Each relative cell viability following IR (mean $\pm$ S.E., $n \geq 4$) is presented as the MLuc activity of irradiated cells relative to those miRNA transfected non-irradiated cells. The dashed line indicates control cell viability following IR.

[0049] **Fig. 11** is a graph showing miRNA mediated radiation sensitization in PC3-MLuc cells. PC3-MLuc Clonogenic Assay. PC3-MLuc cells were transfected with 20 nM of miR-890-5p or control miRNA (cel-miR-239b) and grown for 2 days, after which cells were irradiated at the indicated doses. The cells were grown for 14 days and colonies with greater than 30 cells were scored, and surviving fraction was calculated (mean $\pm$ S.D., $n=3$). *, $P < 0.05$ relative to control. DMF; Dose Modifying Factor.

[0050] **Fig. 12** is an image of western blot analyses demonstrating the knock-down efficacy of target genes by miR-890-5p and MAD2L2 siRNA. LNCaP cells were transfected with 20 nM of control, miR-890-5p mimics or serial dilutions of MAD2L2 siRNA and were incubated for 48 h. Western blot analyses were performed to detect MAD2L2 and WEE1. ACTB was used as a control for protein loading.

[0051] **Figs. 13A-E** are graphs of individual DU145 tumor growth curves. Subcutaneous DU145 tumors were directly injected with PBS, liposomal control miRNA mimetic, or liposomal miR-890-5p mimetic on day -2. On day 0, animals were divided into groups that received either 6 Gy IR or non-irradiated. Tumors were measured every other day and individual tumor growth curves are reported. (**Fig. 13A**) PBS ($n=3$); (**Fig. 13B**) Control miRNA ($n=4$); (**Fig. 13C**) miR-890-5p ($n=5$); (**Fig. 13D**) Control miRNA + IR ($n=4$); (**Fig. 13E**) miR-890-5p + IR ($n=4$).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0052] siRNA library screening has been utilized to determine the influence of DDR genes on prostate cancer sensitivity to IR (Ni X, et al. (2011) J Clin Invest 121(6):2383-2390.). Potent target genes DNAPK, MAD2L2 and BRCA2 were identified, all of which are components of DNA DSB repair. In addition to these genes, RAD23B, a component of

nucleotide excision repair, significantly sensitized cells to IR. These studies demonstrate the utility of high-throughput radiation sensitivity screens to identify vital genes in DNA repair and radiation response. Described herein is a design that examined the role of non-coding microRNA (miRNA) genes in cellular DNA repair and sensitivity to IR.

[0053] miRNAs are small non-coding RNAs which post-transcriptionally regulate gene expression through interaction with the 3' untranslated regions (3'UTRs) of mRNAs. While miRNAs mediate a variety of normal developmental and physiological processes, their expression is commonly deregulated in cancer (Calin GA, Croce CM (2006) *Nat Rev Cancer* 6(11):857-866.). Notably, individual miRNAs have been shown to possess tumor suppressor and oncogenic properties (Kent OA, Mendell JT (2006) *Oncogene* 25(46):6188-6196.). Growing evidence also supports that miRNA genes are responsive to DNA damage and that they can regulate DDR pathways (Zhao L, Bode AM, Cao Y, Dong Z (2012) *Carcinogenesis* 33(11):2220-2227.; Czochoz JR, Glazer PM (2014) *Antioxid Redox Signal* 21(2):293-312.). However, prior to the invention described herein, the role of miRNAs in DNA repair was not fully elucidated. The present disclosure details a high-throughput functional screen of miRNA mimetics to identify candidate miRNAs which altered DNA repair and cellular sensitivity to IR. The resulting miRNAs and pathways are useful in the future radiologic management of cancer patients.

[0054] miRNAs target complementary mRNA through the binding of a small 'seed' recognition sequence, often comprising 6-8 nucleotides (Friedman RC, Farh KK, Burge CB, Bartel DP (2009) *Genome Res* 19(1):92-105.). From this, it is calculable that a single miRNA can regulate hundreds of different of genes (Lewis BP, Burge CB, Bartel DP (2005) *Cell* 120(1):15-20.). On the other hand, it is generally accepted that most miRNAs regulate a few key genes or pathways to achieve a given phenotype. Prior to the invention described herein, there were few studies to characterize the polyvalent nature of a single miRNA within a specific pathway or phenotype. Studies described herein have uncovered two miRNAs, miR-890-5p and miR-744-3p, which regulate multiple components of DNA damage repair to contribute to cellular IR sensitivity. Pre-treatment of established tumors with miR-890-5p mimetics significantly enhanced IR efficacy, demonstrating its potential as an IR-sensitizing agent.

[0055] The present disclosure describes a systematic screen of 810 different miRNA mimetics for the ability to alter DNA damage response caused by ionizing radiation. A comprehensive analysis of miRNA-induced changes in prostate cancer cell growth, survival

and radiosensitivity is described herein. Two potent radiosensitizing miRNAs, miR-890-5p and miR-744-3p, were identified and shown to inhibit DNA repair. Each miRNA targets multiple components of the DNA damage response. As described in detail below, miR-890-5p demonstrated superior radiosensitization when compared to an siRNA against a primary target, MAD2L2. Moreover, MAD2L2 knock-down was not sufficient to ablate miR-890-5p radiosensitization, indicating that additional targets beyond MAD2L2 contribute to the radiosensitization phenotype. These results validate the polyvalent nature of miRNA-regulated pathways and support the use of miR-890-5p as a radiosensitizing agent. DDR pathways influence cellular sensitivity to IR. Growing evidence supports that miRNAs are involved in DDR and repair (Zhao L, Bode AM, Cao Y, Dong Z (2012) *Carcinogenesis* 33(11):2220-2227; Czochor JR, Glazer PM (2014) *Antioxid Redox Signal* 21(2):293-312). The inventors hypothesized that additional DNA repair modifying miRNAs could be identified through a high-throughput screen of miRNA mimetics for the ability to modify cell response to IR. Disclosed herein are data demonstrating that two potent radiation sensitizing miRNAs, miR-890-5p and miR-744-3p, specifically target multiple components of DSB repair, nucleotide excision repair and cell cycle progression checkpoints. These miRNAs were among 324 candidate radiation sensitizing miRNAs and 75 candidate radiation protective miRNAs identified in the screen. As described in detail below, the data is evaluated for previously reported DDR miRNAs. In the same way, the data from non-irradiated cells is analyzed for miRNAs reported in cell growth and cell survival pathways. Multiple miRNAs have been reported to regulate DDR. A number of these miRNAs were found through transcriptional responses to IR treatment or through differential expression in IR-resistant cancer cells (Czochor JR, Glazer PM (2014) *Antioxid Redox Signal* 21(2):293-312; Weidhaas JB, et al. (2007) *Cancer Res* 67(23):11111-11116.; Jossion S, Sung SY, Lao K, Chung LW, Johnstone PA (2008) *Prostate* 68(15):1599-1606.; Chen G, et al. (2010) *Oncol Rep* 23(4):997-1003.; Wagner-Ecker M, Schwager C, Wirkner U, Abdollahi A, Huber PE (2010) *Radiat Oncol* 5:25.; Wang XC, et al. (2011) *Lung Cancer* 72(1):92-99.; Li B, et al. (2011) *Prostate* 71(6):567-574.; Qu C, et al. (2012) *Cell Cycle* 11(4):785-796.; Mueller AC, Sun D, Dutta A (2013) *Oncogene* 32(9):1164-1172.). For example, the miR-34 gene family is induced by IR through direct transcriptional activation by p53. Elevated miR-34 expression results in decreased cellular proliferation and increased apoptosis (He L, et al. (2007) *Nature* 447(7148):1130-1134.; Chang TC, et al. (2007) Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell* 26(5):745-752.; Ji

Q, et al. (2009) *PLoS One* 4(8):e6816.). In the screen of the present disclosure, miR-34c was identified as the most toxic of the 810 miRNAs transfected in the absence of irradiation. Candidate DDR regulating miRNAs have also been found through *in silico* analyses of known DNA repair pathway genes. For example, miR-421 and miR-101 were identified as ATM and DNAPK targeting miRNAs through 3'UTR analyses (Hu H, Du L, Nagabayashi G, Seeger RC, Gatti RA (2010) *Proc Natl Acad Sci USA* 107(4):1506-1511.; Yan D, et al. (2010) *PLoS One* 5(7):e11397.). Both of these reported IR-sensitizing miRNAs were identified as strong radiation sensitizing miRNAs in screens described herein (Table 1).

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-let-7a	MI0000060	UGAGGUAGUAGGUUGUAUAGUU	0.8041	0.0084	0.5011	0.0124	-	1.
hsa-let-7a	MI0000062	UGAGGUAGUAGGUUGUAUAGUU	0.8539	0.0038	0.6082	0.0791	-	2.
hsa-let-7a	MI0000061	UGAGGUAGUAGGUUGUAUAGUU	1.0826	0.0202	1.5569	0.0473	-	3.
hsa-let-7a*	MI0000060	CUAUACAACUACUGUCUUUC	0.9774	0.0624	0.7869	0.0261	-	4.
hsa-let-7a*	MI0000062	CUAUACAACUACUGUCUUUC	0.9802	0.0709	1.3474	0.1846	-	5.
hsa-let-7b	MI0000063	UGAGGUAGUAGGUUGUGUGUU	0.9439	0.0042	0.5533	0.0420	-	6.
hsa-let-7b*	MI0000063	CUAUACAACUACUGCCUUCCC	0.6899	0.0074	0.3826	0.0070	IR sensitizing	7.
hsa-let-7c	MI0000064	UGAGGUAGUAGGUUGUAUUGUU	1.0407	0.0271	0.9334	0.0421	-	8.
hsa-let-7c*	MI0000064	UAGAGUUACACCCUGGGAGUUA	0.7000	0.0034	0.6052	0.0900	-	9.
hsa-let-7d	MI0000065	AGAGGUAGUAGGUUGCAUAGUU	0.7550	0.0179	0.2740	0.0161	IR sensitizing	10.
hsa-let-7d*	MI0000065	CUAUCGACCUGCUGCCUUUCU	0.7337	0.0123	0.6885	0.1232	-	11.
hsa-let-7e	MI0000066	UGAGGUAGGAGGUUGUAUAGUU	0.8641	0.0204	0.2998	0.0470	IR sensitizing	12.
hsa-let-7e*	MI0000066	CUAUCGGGCCUCCUAGCUUCC	0.8050	0.0187	0.5513	0.0620	-	13.
hsa-let-7f	MI0000067	UGAGGUAGUAGAUUGUAUAGUU	0.8799	0.0152	0.2869	0.0310	IR sensitizing	14.
hsa-let-7f	MI0000068	UGAGGUAGUAGAUUGUAUAGUU	0.7732	0.0135	0.2891	0.0176	IR sensitizing	15.
hsa-let-7f-1*	MI0000067	CUAUACAACUACUAGCCUUCCC	0.6366	0.0256	0.1031	0.0117	IR sensitizing	16.
hsa-let-7f-2*	MI0000068	CUAUACAGUCUACUGUCUUCC	0.7062	0.0067	0.6177	0.0489	-	17.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-let-7g	MI0000433	UGAGGUAGUAGUUUGUACAGUU	0.7924	0.0041	0.2524	0.0251	IR sensitizing	18.
hsa-let-7g*	MI0000433	CUGUACAGGCCACUGCCUUGC	0.1979	0.0551	0.0757	0.0055	Toxic	19.
hsa-let-7i	MI0000434	UGAGGUAGUAGUUUGUGCUGUU	0.7524	0.0316	0.2350	0.0363	IR sensitizing	20.
hsa-let-7i*	MI0000434	CUGCGCAAGCUACUGCCUUGCU	0.7183	0.0646	0.3437	0.0509	IR sensitizing	21.
hsa-miR-1	MI0000437	UGGAAUGUAAAGAAAGUAUGUAU	0.5377	0.0214	0.1247	0.0071	IR sensitizing	22.
hsa-miR-1	MI0000651	UGGAAUGUAAAGAAAGUAUGUAU	0.4341	0.0048	0.1000	0.0051	Toxic	23.
hsa-miR-100	MI0000102	AACCCGUAGAUCCGAAACUUGUG	0.8983	0.0174	0.3812	0.0137	IR sensitizing	24.
hsa-miR-100*	MI0000102	CAAGCUUGUAUCUAUAGGUAUG	0.7503	0.0199	2.2564	0.2427	IR protective	25.
hsa-miR-101	MI0000739	UACAGUACUGUGAUAAACUGAA	0.6885	0.0202	0.1710	0.0131	IR sensitizing	26.
hsa-miR-101	MI0000103	UACAGUACUGUGAUAAACUGAA	0.6846	0.0044	0.4206	0.0536	IR sensitizing	27.
hsa-miR-101*	MI0000103	CAGUUAUCACAGUGCUGAUGCU	0.4609	0.0499	0.0519	0.0042	Toxic	28.
hsa-miR-103	MI0000109	AGCAGCAUUGUACAGGCUAUGA	0.7369	0.0019	0.2020	0.0284	IR sensitizing	29.
hsa-miR-103	MI0000108	AGCAGCAUUGUACAGGCUAUGA	0.7492	0.0633	0.2078	0.0077	IR sensitizing	30.
hsa-miR-105	MI0000112	UCAAUUGCUCAGACUCCUGUGGU	0.8355	0.0106	0.2478	0.0228	IR sensitizing	31.
hsa-miR-105	MI0000111	UCAAUUGCUCAGACUCCUGUGGU	0.8607	0.0051	0.2534	0.0139	IR sensitizing	32.
hsa-miR-105*	MI0000112	ACGGAUUGUUGAGCAUGGCUA	0.5136	0.0268	0.1447	0.0222	IR sensitizing	33.
hsa-miR-105*	MI0000111	ACGGAUUGUUGAGCAUGGCUA	0.4246	0.0183	0.1631	0.0044	Toxic	34.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-106a	MI0000113	AAAAGUGCUUACAGUCAGGUAG	1.0258	0.0231	1.8400	0.0309	-	35.
hsa-miR-106a*	MI0000113	CUGCAAUGUAAAGCACUUCUAC	0.4557	0.0070	0.0617	0.0040	Toxic	36.
hsa-miR-106b	MI0000734	UAAAAGUGCUGACAGUCAGAU	1.0790	0.0177	3.9404	0.7860	IR protective	37.
hsa-miR-106b*	MI0000734	CCGCACUGUGGGUACUUGCUGC	0.7654	0.0133	0.6435	0.0177	-	38.
hsa-miR-107	MI0000114	AGCAGCAUUGUACAGGCUAUCA	0.7571	0.0281	0.3698	0.0131	IR sensitizing	39.
hsa-miR-10a	MI0000266	UACCCUGUAGAUCCGAAUUUGUG	0.7258	0.0527	0.1114	0.0082	IR sensitizing	40.
hsa-miR-10a*	MI0000266	CAAUUCGUACUAGGGGAAUA	0.6891	0.0139	0.3067	0.0652	IR sensitizing	41.
hsa-miR-10b	MI0000267	UACCCUGUAGAACCGAAUUUGUG	0.7509	0.0367	0.4434	0.0913	IR sensitizing	42.
hsa-miR-10b*	MI0000267	ACAGAUUCGAUUCUAGGGGAAU	0.7432	0.0079	0.2153	0.0147	IR sensitizing	43.
hsa-miR-122*	MI0000442	AACGCCAUUACACACUAAAUA	0.7535	0.0198	0.3385	0.0118	IR sensitizing	44.
hsa-miR-1224-3p	MI0003764	CCCCACCUCCUCUCUCCUCAG	1.0097	0.0043	2.0936	0.0223	IR protective	45.
hsa-miR-1224-5p	MI0003764	GUGAGGACUCGGGAGGUGG	0.8604	0.0071	1.0604	0.0292	-	46.
hsa-miR-1225-3p	MI0006311	UGAGCCCCUGUGCCGCCCCAG	0.9533	0.0088	1.3683	0.2551	-	47.
hsa-miR-1225-5p	MI0006311	GUGGGUACGGCCAGUGGGGGG	0.9619	0.0151	1.7482	0.0148	-	48.
hsa-miR-1226	MI0006313	UACACGCCUCUGUUUCCCUAG	0.8137	0.0061	0.1391	0.0102	IR sensitizing	49.
hsa-miR-1226*	MI0006313	GUGAGGGCAUGCAGGCCUUGGAGGGG	0.8862	0.0269	0.4958	0.1015	IR sensitizing	50.
hsa-miR-1227	MI0006316	CGUGCCACCCUUUUUCCCCAG	0.9856	0.0040	0.8686	0.0522	-	51.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-1228	MI0006318	UCACACCUGCCUCGCCCCC	0.7914	0.0192	0.1245	0.0094	IR sensitizing	52.
hsa-miR-1228*	MI0006318	GUGGGCGGGGAGGUGUGUG	0.8905	0.0076	1.4090	0.0255	-	53.
hsa-miR-1229	MI0006319	CUCUCACCAUGCCUCCACAG	0.9422	0.0279	2.2888	0.0961	IR protective	54.
hsa-miR-122a	MI0000442	UGGAGUGACAAUGGUGUUUG	0.3429	0.0173	0.0742	0.0069	Toxic	55.
hsa-miR-1231	MI0006321	GUGUCUGGGCGGACAGCUGC	0.1999	0.0347	0.1333	0.0222	Toxic	56.
hsa-miR-1233	MI0006323	UGAGCCUUGUCCUCCCGCAG	0.8152	0.0179	0.4917	0.0721	IR sensitizing	57.
hsa-miR-1234	MI0006324	UCGGCCUGACCAACCCACCCAC	0.8020	0.0128	1.0739	0.0884	-	58.
hsa-miR-1236	MI0006326	CCUCUCCCCUUGUCUCCAG	0.9142	0.0065	2.4281	0.1518	IR protective	59.
hsa-miR-1237	MI0006327	UCCUUCUGCUCCGUCUCCCGCAG	0.6807	0.0175	0.7607	0.0366	-	60.
hsa-miR-1238	MI0006328	CUUCCUUGUCUGUCUCCCGC	0.7790	0.0123	0.2485	0.0357	IR sensitizing	61.
hsa-miR-124*	MI0000445	CGUGUUCACAGCGGACCUUGAU	0.6167	0.0068	0.1184	0.0272	IR sensitizing	62.
hsa-miR-124*	MI0000443	CGUGUUCACAGCGGACCUUGAU	0.7919	0.0243	0.1527	0.0025	IR sensitizing	63.
hsa-miR-124*	MI0000444	CGUGUUCACAGCGGACCUUGAU	0.5555	0.0763	0.4234	0.0701	IR sensitizing	64.
hsa-miR-124a	MI0000443	UAAAGGCACGCGUGAAUGCC	0.2259	0.0094	0.0813	0.0083	Toxic	65.
hsa-miR-124a	MI0000445	UAAAGGCACGCGUGAAUGCC	0.2996	0.0328	0.0727	0.0058	Toxic	66.
hsa-miR-124a	MI0000444	UAAAGGCACGCGUGAAUGCC	0.3045	0.0298	0.0734	0.0048	Toxic	67.
hsa-miR-125a	MI0000469	UCCUGAGACCCUUUAACCUUGA	0.6538	0.0163	1.8782	0.0619	-	68.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-125a-3p	MI0000469	ACAGGUGAGGUUCUUGGGAGCC	0.9197	0.1087	0.7256	0.1533	-	69.
hsa-miR-125b	MI0000446	UCCCUAGAGACCCUAAACUUGUGA	0.6548	0.0378	1.1348	0.0734	-	70.
hsa-miR-125b	MI0000470	UCCCUAGAGACCCUAAACUUGUGA	0.6563	0.0152	1.4880	0.2437	-	71.
hsa-miR-125b-1*	MI0000446	ACGGGUUAGGUCUCUUGGGAGCU	0.7647	0.0217	0.2458	0.0068	IR sensitizing	72.
hsa-miR-125b-2*	MI0000470	UCACAAGUCAGGCUCUUGGGAC	0.9972	0.1009	4.6357	0.9417	IR protective	73.
hsa-miR-126	MI0000471	UCGUACCGUGAGUAAUAAUGCG	1.0571	0.0117	0.5000	0.1012	IR sensitizing	74.
hsa-miR-126*	MI0000471	CAUUAUUACUUUUUGUACGCG	0.7301	0.0119	0.4610	0.1073	IR sensitizing	75.
hsa-miR-127	MI0000472	UCGGAUCCGUCUGAGCUUGGCU	0.4104	0.0265	0.1072	0.0047	Toxic	76.
hsa-miR-127-5p	MI0000472	CUGAAGCUCAGAGGGCUCUGAU	0.5921	0.0562	0.2370	0.0483	IR sensitizing	77.
hsa-miR-128	MI0000727	UCACAGUGAACCGGUCUCUUU	0.9270	0.0241	1.3883	0.1277	-	78.
hsa-miR-128a	MI0000447	UCACAGUGAACCGGUCUCUUU	0.8806	0.0043	0.7198	0.0378	-	79.
hsa-miR-129	MI0000473	CUUUUUUGCGGUCUUGGGCUUGC	0.4263	0.0907	0.1287	0.0145	Toxic	80.
hsa-miR-129	MI0000252	CUUUUUUGCGGUCUUGGGCUUGC	0.4323	0.0808	0.0770	0.0096	Toxic	81.
hsa-miR-129*	MI0000252	AAGCCCUUACCCCAAAAAGUUAU	0.5045	0.0348	0.0749	0.0014	IR sensitizing	82.
hsa-miR-129-3p	MI0000473	AAGCCCUUACCCCAAAAAGCAU	0.4807	0.0628	0.1701	0.0302	Toxic	83.
hsa-miR-130a	MI0000448	CAGUGCAAUGUUAAAAGGGCAU	0.8722	0.0410	2.3713	0.2203	IR protective	84.
hsa-miR-130a*	MI0000448	UUCACAUUGUGCUACUGUCUGC	0.7124	0.0034	0.6782	0.1228	-	85.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-130b	MI0000748	CAGUGCAAUGAUGAAAGGGCAU	0.9770	0.0409	0.3931	0.0257	IR sensitizing	86.
hsa-miR-130b*	MI0000748	ACUCUUUCCCGUUGCACUAC	0.5371	0.0373	0.0483	0.0024	IR sensitizing	87.
hsa-miR-132	MI0000449	UAAACAGUCUACAGCCAUGGUCG	0.8417	0.0321	1.0809	0.1279	-	88.
hsa-miR-132*	MI0000449	ACCGUGGCUUUCGAUUGUUAUCU	0.3933	0.1653	0.0476	0.0006	Toxic	89.
hsa-miR-133a	MI0000450	UUUUGGUCCCCUUAACCCAGCUG	0.3645	0.0344	0.0888	0.0017	Toxic	90.
hsa-miR-133a	MI0000451	UUUGGUCCCCUUAACCCAGCUG	0.4087	0.0047	0.1003	0.0117	Toxic	91.
hsa-miR-133b	MI0000822	UUUGGUCCCCUUAACCCAGCUA	0.2571	0.0057	0.0678	0.0082	Toxic	92.
hsa-miR-134	MI0000474	UGUGACUGGUUGAGCAGAGGGG	0.4863	0.0067	0.1321	0.0061	Toxic	93.
hsa-miR-135a	MI0000453	UAUGGCUUUUUUAUCCUAUGUGA	0.6617	0.0191	0.0884	0.0055	IR sensitizing	94.
hsa-miR-135a	MI0000452	UAUGGCUUUUUUAUCCUAUGUGA	0.3111	0.0178	0.0489	0.0033	Toxic	95.
hsa-miR-135a*	MI0000452	UAUAGGGAUUGGAGCCGUGGCG	0.7943	0.0214	0.1906	0.0128	IR sensitizing	96.
hsa-miR-135b	MI0000810	UAUGGCUUUUUAUCCUAUGUGA	0.2949	0.0387	0.0670	0.0053	Toxic	97.
hsa-miR-135b*	MI0000810	AUGUAGGGCUAAAAGCCAUAGGG	0.3620	0.0599	0.0787	0.0117	Toxic	98.
hsa-miR-136	MI0000475	ACUCCAUUUUGUUUUGAUGAUGGA	0.7618	0.0299	0.2456	0.0668	IR sensitizing	99.
hsa-miR-136*	MI0000475	CAUCAUCGUCUCAAAGAGAGUCU	0.2166	0.0284	0.0838	0.0175	Toxic	100.
hsa-miR-137	MI0000454	UUUUUGCUUUAAGAAUACGCGUAG	0.8045	0.0194	0.3669	0.0318	IR sensitizing	101.
hsa-miR-138	MI0000455	AGCUGGUUUGUGAAUACAGCCCG	0.5387	0.0257	0.2812	0.0111	IR sensitizing	102.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-138	MI0000476	AGCUGGUGUUGUGAAUCAGGCCG	0.4689	0.0079	0.2715	0.0191	Toxic	103.
hsa-miR-138-1 *	MI0000476	GCUACUUCACAAACACAGGGCC	0.9918	0.0800	2.6303	0.6601	IR protective	104.
hsa-miR-138-2 *	MI0000455	GCUAUUUCACGACACACAGGGUU	1.0048	0.0143	0.5456	0.0413	-	105.
hsa-miR-139	MI0000261	UCUACAGUGCAGUGUCUCCAG	0.8448	0.0169	1.0647	0.1519	-	106.
hsa-miR-139-3p	MI0000261	GGAGACGCGGCCCUUGUGAGU	0.6889	0.0195	0.6288	0.1835	-	107.
hsa-miR-140	MI0000456	CAGUGGUUUUACCCUUAUGGUAG	0.8117	0.0198	0.2087	0.0146	IR sensitizing	108.
hsa-miR-140-3p	MI0000456	UACCACAGGUAGAACCACGG	1.1001	0.0102	1.4576	0.1591	-	109.
hsa-miR-141	MI0000457	UAACACUGUCUGGUAAGAUGG	0.7707	0.0306	0.6462	0.0853	-	110.
hsa-miR-141 *	MI0000457	CAUCUCCAGUACAGUGUUGGA	0.8234	0.0148	0.2189	0.0160	IR sensitizing	111.
hsa-miR-142-3p	MI0000458	UGUAGUGUUUCCUACUUUAUGGA	0.8772	0.0559	0.3713	0.0310	IR sensitizing	112.
hsa-miR-142-5p	MI0000458	CAUAAAGUAGAAAGCACUACU	0.7510	0.0267	1.3318	0.0615	-	113.
hsa-miR-143	MI0000459	UGAGAUGAAGCACUGUAGCUC	0.6571	0.0083	0.1961	0.0102	IR sensitizing	114.
hsa-miR-143 *	MI0000459	GGUGCAGUCUGCAUCUCUGGU	0.8151	0.0034	1.0073	0.0480	-	115.
hsa-miR-144	MI0000460	UACAGUAUAGAUGAUGUACU	0.7265	0.0192	0.4161	0.0165	IR sensitizing	116.
hsa-miR-144 *	MI0000460	GGUAUCAUCAUAUCUGUAAG	0.6358	0.0753	0.2359	0.0087	IR sensitizing	117.
hsa-miR-145	MI0000461	GUCCAGUUUCCAGGAUCCCU	0.6547	0.0132	0.3191	0.0494	IR sensitizing	118.
hsa-miR-145 *	MI0000461	GGAUUCCUGGAAAUACUGUUCU	0.8760	0.1298	4.8001	1.5232	IR protective	119.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-146a	MI0000477	UGAGAACUGAAUCCAUUGGGUU	0.7096	0.0566	0.2440	0.0409	IR sensitizing	120.
hsa-miR-146a*	MI0000477	CCUCUGAAAUUCAGUUCUUCAG	1.0002	0.0788	2.2984	0.0838	IR protective	121.
hsa-miR-146b	MI0003129	UGAGAACUGAAUCCAUAGGCU	0.9191	0.0056	0.2987	0.0301	IR sensitizing	122.
hsa-miR-146b-3p	MI0003129	UGCCUUGUGGACUCAGUUCUGG	0.6385	0.0100	1.6192	0.0912	-	123.
hsa-miR-147	MI0000262	GUGUGUGGAAUUGCUUCUCG	0.7001	0.0178	1.1967	0.0906	-	124.
hsa-miR-147b	MI0005544	GUGUGCGGAAUUGCUUCUCGUA	0.8968	0.0155	0.5854	0.0693	-	125.
hsa-miR-148a	MI0000253	UCAGUGCACUACAGAACUUUGU	0.9991	0.0228	0.9673	0.1019	-	126.
hsa-miR-148a*	MI0000253	AAAGUUCUGAGACACUCCGACU	0.7722	0.0040	0.6838	0.0426	-	127.
hsa-miR-148b	MI0000811	UCAGUGCAUCACAGAACUUUGU	0.8526	0.0268	0.5226	0.0392	-	128.
hsa-miR-148b*	MI0000811	AAGUUCUGUUAUACACUCAGGC	0.5011	0.0154	0.1069	0.0075	IR sensitizing	129.
hsa-miR-149	MI0000478	UCUGGCUCCGUGUCUUCACUCCC	0.8050	0.0072	0.5235	0.0808	-	130.
hsa-miR-149*	MI0000478	AGGGAGGACGGGGGCGUGGC	0.5380	0.0521	0.2459	0.0263	IR sensitizing	131.
hsa-miR-150	MI0000479	UCUCCCAACCCUUGUACACAGUG	0.7342	0.0352	0.8894	0.1537	-	132.
hsa-miR-150*	MI0000479	CUGGUACAGGCCUGGGGGACAG	0.9845	0.0794	2.6782	0.1093	IR protective	133.
hsa-miR-151	MI0000809	CUAGACUGAAGCUCCUUGAGG	0.7966	0.0158	0.2138	0.0147	IR sensitizing	134.
hsa-miR-151-5p	MI0000809	UCGAGGAGCUCACAGUCUAGU	0.3911	0.0753	0.4896	0.1060	Toxic	135.
hsa-miR-152	MI0000462	UCAGUGCAUGACAGAACUUGG	0.7439	0.0249	0.5946	0.0321	-	136.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-153	MI0000463	UUGCAUAGUCACAAAAGUGAUC	0.3778	0.0468	0.0520	0.0031	Toxic	137.
hsa-miR-153	MI0000464	UUGCAUAGUCACAAAAGUGAUC	0.3808	0.0082	0.0443	0.0022	Toxic	138.
hsa-miR-154	MI0000480	UAGGUUAUCCGUGUUGCCUUCG	0.6328	0.0572	0.1059	0.0180	IR sensitizing	139.
hsa-miR-154*	MI0000480	AAUCAUACACGGUUGACCUAUU	0.7065	0.0268	0.3843	0.0240	IR sensitizing	140.
hsa-miR-155	MI0000681	UUAAUAGCUAAUCGUGAUAGGGGU	0.6851	0.0262	0.5770	0.0160	—	141.
hsa-miR-155*	MI0000681	CUCCUACAUUUAGCAUUUACA	0.7936	0.0132	1.4928	0.0445	—	142.
hsa-miR-15a	MI0000069	UAGCAGCACAUAAUGGUUUGUG	0.3351	0.0077	0.0535	0.0024	Toxic	143.
hsa-miR-15a*	MI0000069	CAGGCCAUUUUGUGUGCCUCA	0.6242	0.0152	0.3361	0.0504	IR sensitizing	144.
hsa-miR-15b	MI0000438	UAGCAGCACAUCAUUGGUUUACA	0.3339	0.0021	0.0671	0.0088	Toxic	145.
hsa-miR-15b*	MI0000438	CGAAUCAUUUUUGUGUCUCUA	1.0552	0.0401	3.2178	0.3787	IR protective	146.
hsa-miR-16	MI0000115	UAGCAGCACGUAAAUUUGGCG	0.6786	0.1051	0.0842	0.0093	IR sensitizing	147.
hsa-miR-16	MI0000070	UAGCAGCACGUAAAUUUGGCG	0.2514	0.0840	0.0384	0.0022	Toxic	148.
hsa-miR-16-1*	MI0000070	CCAGUAAUUAACUGUGCUGCUGA	0.6827	0.0119	1.1763	0.2622	—	149.
hsa-miR-16-2*	MI0000115	CCAAUAAUUAACUGUGCUGCUUUA	0.7163	0.0051	0.4185	0.0152	IR sensitizing	150.
hsa-miR-17-3p	MI0000071	ACUGCAGUAGAGGACUUGUAG	0.7322	0.0196	0.4307	0.0465	IR sensitizing	151.
hsa-miR-17-5p	MI0000071	CAAAUGUCUUACAGUCAGGUAG	0.8932	0.0157	1.1356	0.2616	—	152.
hsa-miR-181a	MI0000289	AACAUUCAACGUGUGGUGAGU	0.8346	0.0322	0.1738	0.0177	IR sensitizing	153.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-181a	MI0000269	AACAUUCAACGUGUCGGUGAGU	0.8435	0.0215	0.2398	0.0116	IR sensitizing	154.
hsa-miR-181a-2*	MI0000269	ACCACUGACCGUUGACUGUACC	0.7755	0.0073	1.2687	0.1001	—	155.
hsa-miR-181b	MI0000270	AACAUUCAUUGCUGCGUGGGU	0.7842	0.0052	0.5033	0.0442	—	156.
hsa-miR-181b	MI0000683	AACAUUCAUUGCUGCGUGGGU	0.7746	0.0150	0.5445	0.0288	—	157.
hsa-miR-181c	MI0000271	AACAUUCAACCGUGCGUGAGU	0.6438	0.0365	0.2587	0.0165	IR sensitizing	158.
hsa-miR-181c*	MI0000271	AACCAUCGACCGUUGAGUGGAC	0.2524	0.0437	0.2070	0.0393	Toxic	159.
hsa-miR-181d	MI0003139	AACAUUCAUUGUUGCGUGGGU	0.8900	0.0094	0.6879	0.1043	—	160.
hsa-miR-182	MI0000272	UUUGGCAUUGGUAGAACUCACACU	0.7557	0.0060	0.7695	0.0280	—	161.
hsa-miR-182*	MI0000272	UGGUUCUAGACUUGCCAAACUA	0.2430	0.0335	0.0757	0.0060	Toxic	162.
hsa-miR-183	MI0000273	UAUGGCACUGGUAGAAUUCACU	0.2110	0.0294	0.0658	0.0046	Toxic	163.
hsa-miR-183*	MI0000273	GUGAAUUAACCGAAGGGCCAUAA	0.6406	0.0484	0.2805	0.0473	IR sensitizing	164.
hsa-miR-184	MI0000481	UGGACGGAGAACUGAUAAAGGGU	0.2049	0.0186	0.0548	0.0043	Toxic	165.
hsa-miR-185	MI0000482	UGGAGAGAAAGGCAGUUCUGA	0.1253	0.0106	0.0522	0.0029	Toxic	166.
hsa-miR-185*	MI0000482	AGGGGCGGCUUUCUCCUCUGGUC	0.2913	0.0318	0.0734	0.0040	Toxic	167.
hsa-miR-186	MI0000483	CAAAGAAUUCUCCUUUUGGGCU	0.7772	0.0138	0.6923	0.0313	—	168.
hsa-miR-186*	MI0000483	GCCCCAAAGGUGAAUUUUUGGG	0.7949	0.0225	1.6348	0.2281	—	169.
hsa-miR-187	MI0000274	UCGUGUCUUGUUGCAGCCGG	0.7899	0.0055	0.5550	0.0248	—	170.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-187*	MI0000274	GGCUACAACACAGGACCCGGGC	0.8707	0.0190	1.6240	0.1864	—	171.
hsa-miR-188	MI0000484	CAUCCCUUGCAUGGUGGAGGG	0.8175	0.0086	0.7912	0.0285	—	172.
hsa-miR-188-3p	MI0000484	CUCCCAUAGCAGGUUUUGCA	0.7766	0.0070	1.0087	0.1290	—	173.
hsa-miR-189	MI0000080	UGCCUACUGAGCUGAUUUCAGU	0.6842	0.0038	0.5770	0.1366	—	174.
hsa-miR-18a	MI0000072	UAAAGGUGCAUCUAGUGCAGAUAG	0.8138	0.0101	0.3623	0.0374	IR sensitizing	175.
hsa-miR-18a*	MI0000072	ACUGCCCUAAGUGCUCCUUCUGG	0.7276	0.0041	0.6274	0.0584	—	176.
hsa-miR-18b	MI0001518	UAAAGGUGCAUCUAGUGCAGAUAG	0.7583	0.0023	0.3197	0.0129	IR sensitizing	177.
hsa-miR-18b*	MI0001518	UGCCCUAAAUGCCCCUUCUGGC	0.6900	0.0183	0.7755	0.1860	—	178.
hsa-miR-190	MI0000486	UGAU AUGUUUGAUUAUUAGGU	0.6262	0.0414	0.1423	0.0067	IR sensitizing	179.
hsa-miR-190b	MI0005545	UGAU AUGUUUGAUUAUUGGGUU	0.6573	0.0498	0.2189	0.0382	IR sensitizing	180.
hsa-miR-191	MI0000465	CAACGGAAUCCCAAAAGCAGCUG	0.7225	0.0109	0.4522	0.0129	IR sensitizing	181.
hsa-miR-191*	MI0000465	GCUGCGCUUGGAUUUCGUCCCC	1.1864	0.0273	3.2168	0.6197	IR protective	182.
hsa-miR-192	MI0000234	CUGACCUAUGAAUUGACAGCC	0.9028	0.0381	0.3292	0.0140	IR sensitizing	183.
hsa-miR-192*	MI0000234	CUGCCAAUUCUUAUAGGUCACAG	0.7635	0.0169	0.4231	0.1182	IR sensitizing	184.
hsa-miR-193a	MI0000487	AACUGGCCUACAAAGUCCAGU	0.1215	0.0321	0.0461	0.0067	Toxic	185.
hsa-miR-193a-5p	MI0000487	UGGGUCUUUGCGGGCAGAUAGA	0.5396	0.0384	0.2588	0.0436	IR sensitizing	186.
hsa-miR-193b	MI0003137	AACUGGCCCUCAAAGUCCCGCU	0.4375	0.0343	0.1433	0.0455	Toxic	187.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-193b*	MI0003137	CGGGGUUUUGAGGGCGAGAUGA	0.2389	0.0341	0.1880	0.0249	Toxic	188.
hsa-miR-194	MI0000732	UGUAAACAGCAACUCCAUGUGGA	0.7185	0.0080	0.6237	0.0234	—	189.
hsa-miR-194	MI0000488	UGUAAACAGCAACUCCAUGUGGA	0.8403	0.0172	0.7118	0.1351	—	190.
hsa-miR-194*	MI0000732	CCAGUGGGGUGUGUUUAUCUG	0.6732	0.0151	0.5545	0.0093	—	191.
hsa-miR-195	MI0000489	UAGCAGCACAGAAAUUUGGC	0.1668	0.0159	0.0442	0.0026	Toxic	192.
hsa-miR-195*	MI0000489	CCAAUUAUUGGUGUGUCGUCC	0.9332	0.0378	2.1295	0.4623	IR protective	193.
hsa-miR-196a	MI0000279	UAGGUAGUUUCAUGUUGUUGGG	0.6660	0.0378	0.1354	0.0164	IR sensitizing	194.
hsa-miR-196a	MI0000238	UAGGUAGUUUCAUGUUGUUGGG	0.5845	0.0247	0.1661	0.0127	IR sensitizing	195.
hsa-miR-196a*	MI0000279	CGGCAACAAGAAACUGCCUGAG	0.7403	0.0076	0.1755	0.0166	IR sensitizing	196.
hsa-miR-196b	MI0001150	UAGGUAGUUUCCUGUUGUUGGG	0.5182	0.0334	0.1262	0.0059	IR sensitizing	197.
hsa-miR-197	MI0000239	UUCACCACCUUCUCCACCCAGC	0.5603	0.0530	0.1521	0.0164	IR sensitizing	198.
hsa-miR-198	MI0000240	GGUCCAGAGGGGAGAUAGGUUC	0.7814	0.0131	0.6914	0.0389	—	199.
hsa-miR-199a	MI0000242	CCCAGUGUUCAGACUACCUGUUC	0.8547	0.0077	0.3023	0.0440	IR sensitizing	200.
hsa-miR-199a	MI0000281	CCCAGUGUUCAGACUACCUGUUC	0.8296	0.0149	0.4195	0.0587	IR sensitizing	201.
hsa-miR-199a*	MI0000242	ACAGUAGUCUGCACAUUGGUUA	0.6963	0.0108	0.1556	0.0325	IR sensitizing	202.
hsa-miR-199a*	MI0000281	ACAGUAGUCUGCACAUUGGUUA	0.6344	0.0055	0.1793	0.0183	IR sensitizing	203.
hsa-miR-199b	MI0000282	CCCAGUUGUUAGACUACUUGUUC	0.9481	0.0170	0.8395	0.2199	—	204.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-199b-3p	MI0000282	ACAGUAGUCUGCACAUUGGUUA	0.6038	0.0069	0.1767	0.0046	IR sensitizing	205.
hsa-miR-19a	MI0000073	UGUGCAAAUUCUAUGCAAAACUGA	1.1559	0.0166	2.1580	0.1567	IR protective	206.
hsa-miR-19a*	MI0000073	AGUUUUGCAUAGUUGCACUACA	0.7516	0.0060	0.1632	0.0471	IR sensitizing	207.
hsa-miR-19b	MI0000075	UGUGCAAAUCCAUUGCAAAACUGA	0.7908	0.0033	0.5063	0.0641	-	208.
hsa-miR-19b	MI0000074	UGUGCAAAUCCAUUGCAAAACUGA	1.1556	0.0158	1.7764	0.0951	-	209.
hsa-miR-19b-1*	MI0000074	AGUUUUGCAGGUUUGCAUCCAGC	0.3064	0.0389	0.0762	0.0171	Toxic	210.
hsa-miR-19b-2*	MI0000075	AGUUUUGCAGGUUUGCAUUAUA	0.7974	0.0117	0.2561	0.0341	IR sensitizing	211.
hsa-miR-200a	MI0000737	UAACACUGUCUGGUAAACGAUGU	0.7191	0.0029	0.8654	0.0582	-	212.
hsa-miR-200a*	MI0000737	CAUCUUACCGGACAGUCUGGGA	0.5586	0.0108	0.1723	0.0154	IR sensitizing	213.
hsa-miR-200b	MI0000342	UAAUACUGCCUGGUAAUGAUGA	0.6465	0.0129	1.1028	0.1877	-	214.
hsa-miR-200b*	MI0000342	CAUCUUACUGGGCAGCAUUGGA	1.0400	0.0244	1.0418	0.3028	-	215.
hsa-miR-200c	MI0000650	UAAUACUGCCGGUAAUGAUGGA	0.7223	0.0103	0.6592	0.0337	-	216.
hsa-miR-200c*	MI0000650	CGUCUUACCCAGCAGUGUUUGG	0.7621	0.0340	0.5579	0.0416	-	217.
hsa-miR-202	MI0003130	AGAGGUUAAGGGCAUGGGAA	0.7818	0.0070	0.8630	0.2861	-	218.
hsa-miR-202*	MI0003130	UUCCUAGCAUACUUCUUUG	0.7548	0.0287	3.0340	0.4219	IR protective	219.
hsa-miR-203	MI0000283	GUGAAAUUUUAGGACCACUAG	0.8830	0.0041	0.4633	0.0239	IR sensitizing	220.
hsa-miR-204	MI0000284	UUCCCUUUUGUCAUCCUAUGCCU	0.6626	0.0227	0.3020	0.0141	IR sensitizing	221.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-205	MI0000285	UCCUUCAUUCCACCGGAGUCUG	0.7803	0.0066	1.6478	0.0849	-	222.
hsa-miR-206	MI0000490	UGGAAUGUAAGGAAGUGUGUGG	0.4253	0.0190	0.1063	0.0066	Toxic	223.
hsa-miR-208	MI0000251	AUAAGACGAGCAAAAAGCUUGU	0.5488	0.0272	0.1825	0.0082	IR sensitizing	224.
hsa-miR-208b	MI0005570	AUAAGACGAACAAAGGUUUGU	0.2667	0.0027	0.0636	0.0043	Toxic	225.
hsa-miR-20a	MI0000076	UAAAGUGCUUAUAGUCAGGUAG	1.1360	0.0162	3.8424	0.4255	IR protective	226.
hsa-miR-20a*	MI0000076	ACUGCAUUAUGAGCACUUAAAG	0.6851	0.0125	1.3882	0.0696	-	227.
hsa-miR-20b	MI0001519	CAAAAGUGCUCUAUGUCAGGUAG	1.0941	0.0300	4.0617	0.8014	IR protective	228.
hsa-miR-20b*	MI0001519	ACUGUAGUAUGGGCACUUCAG	0.5879	0.0178	0.2601	0.0359	IR sensitizing	229.
hsa-miR-21	MI0000077	UAGCUUAUCAGACUGAUUGUGA	1.0929	0.0223	2.8244	0.0922	IR protective	230.
hsa-miR-21*	MI0000077	CAACACCAAGUCGAUGGGCUGU	0.5042	0.0336	0.2441	0.0448	IR sensitizing	231.
hsa-miR-210	MI0000286	CUGUGCGUGUGACAGCGGCUGA	0.7864	0.0474	0.4375	0.0263	IR sensitizing	232.
hsa-miR-211	MI0000287	UUCCCUUUUGUAUCCUUCGCCU	0.8553	0.0486	0.6871	0.1291	-	233.
hsa-miR-212	MI0000288	UAACAGUCUCCAGUCACGGCC	0.8810	0.0179	0.4752	0.0426	IR sensitizing	234.
hsa-miR-213	MI0000289	ACCAUCGACCGUUGAUUGUACC	0.9688	0.0245	2.2163	0.2105	IR protective	235.
hsa-miR-214	MI0000290	ACAGCAGGCACAGACAGGCAGU	0.6902	0.0142	0.2366	0.0664	IR sensitizing	236.
hsa-miR-214*	MI0000290	UGCCUGUCUACACUUGCUGUGC	0.1295	0.0073	0.0768	0.0065	Toxic	237.
hsa-miR-215	MI0000291	AUGACCUAUGAAUUGACAGAC	0.6567	0.0137	0.2648	0.0078	IR sensitizing	238.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-216	MI0000292	UAAUCUCAGCUGGCAACUGUGA	0.8020	0.0089	0.3836	0.0289	IR sensitizing	239.
hsa-miR-216b	MI0005569	AAAUCUCUGCAGGCAAAUGUGA	0.7647	0.0067	0.2287	0.0250	IR sensitizing	240.
hsa-miR-217	MI0000293	UACUGCAUCAGGAACUGAUUGGA	0.5067	0.0140	0.1320	0.0261	IR sensitizing	241.
hsa-miR-218	MI0000295	UUGUGCUUGAUCUAACCAUGU	0.8539	0.0240	0.5689	0.0309	-	242.
hsa-miR-218	MI0000294	UUUGUCUUGAUCUAACCAUGU	0.6356	0.0189	0.4202	0.0102	IR sensitizing	243.
hsa-miR-218-1*	MI0000294	AUGGUUCCGUC AAGCACC AUGG	0.6901	0.0238	0.2256	0.0307	IR sensitizing	244.
hsa-miR-218-2*	MI0000295	CAUGGUUCUGUCAAGCACC GCG	0.7913	0.0028	0.2207	0.0329	IR sensitizing	245.
hsa-miR-219	MI0000740	UGAUUGUCCAAACGCAAUUCU	0.6526	0.0099	0.2798	0.0035	IR sensitizing	246.
hsa-miR-219	MI0000296	UGAUUGUCCAAACGCAAUUCU	0.7938	0.0245	0.3055	0.0325	IR sensitizing	247.
hsa-miR-219-1-3p	MI0000296	AGAGUUGAGUCUGGACGUC CCG	0.1430	0.0109	0.1022	0.0047	Toxic	248.
hsa-miR-219-2-3p	MI0000740	AGAAUUGUGGCU GGCACAU CUGU	0.8604	0.0581	0.7319	0.1978	-	249.
hsa-miR-22	MI0000078	AAGCUGCCAGUUGAAGAACUGU	0.3114	0.0920	0.1175	0.0106	Toxic	250.
hsa-miR-22*	MI0000078	AGUUCUUCAGUGGCAAGCUUUA	0.5484	0.0061	0.2162	0.0522	IR sensitizing	251.
hsa-miR-220	MI0000297	CCACACCGUAUCUGACACUUU	0.9293	0.0278	3.2974	0.6668	IR protective	252.
hsa-miR-220b	MI0005529	CCACCACCGUCUGACACUU	0.9062	0.0086	2.7272	0.4429	IR protective	253.
hsa-miR-220c	MI0005536	ACACAGGCGUGUUGAAGACU	0.6362	0.0409	0.0798	0.0107	IR sensitizing	254.
hsa-miR-221	MI0000298	AGCUACA UUGUCUGG GGUUC	0.6896	0.0074	0.6464	0.0328	-	255.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-221*	MI0000298	ACCUGGCAUACAAUGUAGAUUU	0.5800	0.0598	0.1428	0.0052	IR sensitizing	256.
hsa-miR-222	MI0000299	AGCUACAUCUGGCUACUGGGU	0.7901	0.0055	0.5577	0.0257	-	257.
hsa-miR-222*	MI0000299	CUCAGUAGCCAGUGUAGAUCCU	0.4253	0.0291	0.0922	0.0017	Toxic	258.
hsa-miR-223	MI0000300	UGUCAGUUUGUCAAAUACCCCA	0.7472	0.0028	0.5337	0.0551	-	259.
hsa-miR-223*	MI0000300	CGUGUAUUUGACAAAGCUGAGUU	0.6696	0.0031	0.1172	0.0158	IR sensitizing	260.
hsa-miR-224	MI0000301	CAAGUCACUAGUGGUUCCGUU	0.7441	0.0265	0.3164	0.0334	IR sensitizing	261.
hsa-miR-23a	MI0000079	AUCACAUUGCCAGGGAUUUCC	1.0995	0.0133	3.2699	0.3492	IR protective	262.
hsa-miR-23a*	MI0000079	GGGUUCCUGGGGAUUGGGAUUU	0.8400	0.0076	2.0516	0.4321	IR protective	263.
hsa-miR-23b	MI0000439	AUCACAUUGCCAGGGAUUUACC	0.6320	0.0190	1.1405	0.0289	-	264.
hsa-miR-23b*	MI0000439	UGGUUCCUGGCAUGCUGAUUU	0.5624	0.0226	0.1454	0.0332	IR sensitizing	265.
hsa-miR-24	MI0000081	UGGUCAGUUCAGCAGGAACAG	0.6465	0.1565	0.1272	0.0088	IR sensitizing	266.
hsa-miR-24	MI0000080	UGGCUCAGUUCAGCAGGAACAG	0.4347	0.0211	0.0988	0.0049	Toxic	267.
hsa-miR-24-2*	MI0000081	UGCCUACUGAGCUGAAACACAG	0.7707	0.0094	0.4175	0.1048	IR sensitizing	268.
hsa-miR-25	MI0000082	CAUUGCACUUGUCUCGGUCUGA	0.9853	0.0157	0.7765	0.0214	-	269.
hsa-miR-25*	MI0000082	AGCGGAGACUUGGGCAAUUG	0.1479	0.0294	0.0311	0.0005	Toxic	270.
hsa-miR-26a	MI00000750	UUCAAAGUAAUCCAGGAUAGGCU	0.3712	0.0566	0.0602	0.0013	Toxic	271.
hsa-miR-26a	MI0000083	UUCAAAGUAAUCCAGGAUAGGCU	0.4137	0.0124	0.1526	0.0255	Toxic	272.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-26a-1*	MI0000083	CCUAUUCUUGGUACUUCGACG	0.8842	0.0107	3.8351	0.5408	IR protective	273.
hsa-miR-26a-2*	MI0000750	CCUAUUCUUGAUACUUGUUUC	0.9425	0.0240	3.5034	0.7091	IR protective	274.
hsa-miR-26b	MI0000084	UUC AAGUAAUUCAGGAUAGGU	0.7972	0.0182	0.3590	0.0238	IR sensitizing	275.
hsa-miR-26b*	MI0000084	CCUGUUCUCCAUACUUGGCUC	0.7031	0.0184	0.3014	0.0156	IR sensitizing	276.
hsa-miR-27a	MI0000085	UUCACAGUGGCUAAGUCCGC	0.8556	0.0157	0.4383	0.0254	IR sensitizing	277.
hsa-miR-27a*	MI0000085	AGGGCUUAGCUGCUUGUGAGCA	0.5316	0.0114	0.0932	0.0064	IR sensitizing	278.
hsa-miR-27b	MI0000440	UUCACAGUGGCUAAGUUCUGC	0.6795	0.0270	0.2697	0.0285	IR sensitizing	279.
hsa-miR-27b*	MI0000440	AGAGCUUAGCUGAUUGGUGAAC	1.0592	0.0147	0.6064	0.0457	-	280.
hsa-miR-28	MI0000086	AAGGAGCUCACAGUCUAUUGAG	0.6853	0.0033	0.1220	0.0147	IR sensitizing	281.
hsa-miR-28-3p	MI0000086	CACUAGAUUGUGAGCUCCUGGA	0.4953	0.0614	0.1655	0.0028	Toxic	282.
hsa-miR-296	MI0000747	AGGGCCCCCUCUAUCCUGU	0.5186	0.0124	0.0988	0.0070	IR sensitizing	283.
hsa-miR-296-3p	MI0000747	GAGGGUUGGGUGAGGCUCUCC	0.7414	0.0187	0.7000	0.0628	-	284.
hsa-miR-297	MI0005775	AUGUUGUGUGCAUGUGCAUG	0.5704	0.0056	0.0825	0.0047	IR sensitizing	285.
hsa-miR-298	MI0005523	AGCAGAAAGCAGGAGGUUCUCCCA	0.8404	0.0139	0.3962	0.0450	IR sensitizing	286.
hsa-miR-299-3p	MI0000744	UAUGUGGGAUGGUAAACCGCUU	0.1463	0.0319	0.0570	0.0065	Toxic	287.
hsa-miR-299-5p	MI0000744	UGGUUUACCGUCCACAUACAU	0.3067	0.0187	0.0869	0.0044	Toxic	288.
hsa-miR-29a	MI0000087	UAGCACCAUCUGAAAUCGGUUA	0.4487	0.0227	0.0832	0.0126	Toxic	289.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-29a*	MI0000087	ACUGAUUUCUUUUUGGUGUUCAG	0.8005	0.0248	0.7675	0.0362	-	290.
hsa-miR-29b	MI0000105	UAGCACCAUUUGAAAUACAGUGUU	0.8178	0.0055	1.8440	0.0362	-	291.
hsa-miR-29b	MI0000107	UAGCACCAUUUGAAAUACAGUGUU	0.7936	0.0088	1.8495	0.0260	-	292.
hsa-miR-29b-1*	MI0000105	GCUGGUUUCAUUUGGUGGUUUAGA	0.7185	0.0237	0.3630	0.0345	IR sensitizing	293.
hsa-miR-29b-2*	MI0000107	CUGGUUUCACAUUGGUGGUUUAG	0.7176	0.0179	0.2194	0.0309	IR sensitizing	294.
hsa-miR-29c	MI0000735	UAGCACCAUUUGAAAUACGGUUA	0.3554	0.0177	0.0598	0.0066	Toxic	295.
hsa-miR-29c*	MI0000735	UGACCGAUUUCUCCUGGUGUUC	0.6483	0.0026	0.2151	0.0364	IR sensitizing	296.
hsa-miR-300	MI0005525	UAUACAAGGCGACACUCUCUCU	0.7892	0.0117	0.8655	0.2202	-	297.
hsa-miR-301	MI0000745	CAGUGCAAUAGUAUUUGUCAAAGC	0.7906	0.0278	0.1390	0.0044	IR sensitizing	298.
hsa-miR-301b	MI0005568	CAGUGCAAUAGUAUUUGUCAAAGC	0.9298	0.0053	0.4716	0.0266	IR sensitizing	299.
hsa-miR-302a	MI0000738	UAAAGUCUUCUCCAUUUUUUGGUGA	0.7384	0.0423	1.1324	0.0790	-	300.
hsa-miR-302a*	MI0000738	ACUUUAAACGUGGAUGUACUUUGCU	0.9927	0.0200	2.1893	0.0699	IR protective	301.
hsa-miR-302b	MI0000772	UAAAGUCUUCUCCAUUUUUUAGUAG	0.7365	0.0035	0.9753	0.0055	-	302.
hsa-miR-302b*	MI0000772	ACUUUAAACGUGGAUGUACUUUGCU	0.9703	0.0214	2.0736	0.0901	IR protective	303.
hsa-miR-302c	MI0000773	UAAAGUCUUCUCCAUUUUUUAGUAG	0.7387	0.0094	0.9733	0.0115	-	304.
hsa-miR-302c*	MI0000773	UUUAAACAUGGGGUACCUUCGUG	0.7561	0.0067	1.1662	0.0394	-	305.
hsa-miR-302d	MI0000774	UAAAGUCUUCUCCAUUUUUUAGUAG	0.7358	0.0040	0.9863	0.0740	-	306.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-302d*	MI0000774	ACUUUAAACAUGGAGGACUUUC	0.8092	0.0071	0.5702	0.0112	-	307.
hsa-miR-30a-3p	MI0000088	CUUUCAGUCGGAUGUUUGCAGC	0.8890	0.0120	0.2354	0.0667	IR sensitizing	308.
hsa-miR-30a-5p	MI0000088	UGUAAACAUCUUCGACUGGAAG	0.3342	0.0422	0.0940	0.0070	Toxic	309.
hsa-miR-30b	MI0000441	UGUAAACAUCUUCACUCAGCU	0.4822	0.0016	0.1182	0.0083	Toxic	310.
hsa-miR-30b*	MI0000441	CUGGGAGGUGGAUGUUUACUUC	0.1087	0.0184	0.0585	0.0061	Toxic	311.
hsa-miR-30c	MI0000736	UGUAAACAUCUUCACUCUCAGC	0.9633	0.0112	3.1998	0.5900	IR protective	312.
hsa-miR-30c	MI0000254	UGUAAACAUCUUCACUCUCAGC	0.4579	0.0718	0.1150	0.0123	Toxic	313.
hsa-miR-30c-1*	MI0000736	CUGGGAGAGGUGUUUACUUC	0.2166	0.0078	0.0648	0.0044	Toxic	314.
hsa-miR-30c-2*	MI0000254	CUGGGAGAGGUGUUUACUUC	0.2768	0.0148	0.0993	0.0331	Toxic	315.
hsa-miR-30d	MI0000255	UGUAAACAUCUUCGACUGGAAG	0.5156	0.0186	0.2170	0.0104	IR sensitizing	316.
hsa-miR-30d*	MI0000255	CUUUCAGUCAGAUUUUGCUGC	0.7844	0.0264	0.2260	0.0453	IR sensitizing	317.
hsa-miR-30e-3p	MI0000749	CUUUCAGUCGGAUGUUUACAGC	0.7817	0.0022	0.6186	0.0902	-	318.
hsa-miR-30e-5p	MI0000749	UGUAAACAUCUUCGACUGGAAG	0.6875	0.0411	0.1747	0.0221	IR sensitizing	319.
hsa-miR-31	MI0000089	AGGCAAGAUUCUGGCAUAGCU	0.7208	0.0090	0.5533	0.0919	-	320.
hsa-miR-31*	MI0000089	UGCUAUGCCCAUAUUGCCAU	0.5977	0.0065	2.3161	0.4223	IR protective	321.
hsa-miR-32	MI0000090	UAUUUGCACAUUACAAAGUUGCA	0.8066	0.0069	0.9308	0.0397	-	322.
hsa-miR-32*	MI0000090	CAAUUAGUGUGUGAUUUU	0.5427	0.0096	0.0634	0.0029	IR sensitizing	323.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-320	MI0000542	AAAAGCUGGUUGAGAGGGCGA	0.6822	0.0025	0.5645	0.1116	-	324.
hsa-miR-323	MI0000807	CACAUUACACGGUCGACCUUCU	0.6604	0.0280	0.0424	0.0022	IR sensitizing	325.
hsa-miR-323-5p	MI0000807	AGGUGUCCGUGGCGGUUCGC	0.2898	0.0288	0.1457	0.0357	Toxic	326.
hsa-miR-324-3p	MI0000813	ACUGCCCCAGGUGCUGCUGG	0.6698	0.0102	0.6562	0.0889	-	327.
hsa-miR-324-5p	MI0000813	CGCAUCCCUAGGGCAUUGGUGU	1.0619	0.0339	2.6122	0.0979	IR protective	328.
hsa-miR-325	MI0000824	CCUAGUAGGUGUCCAGUAAGUGU	1.0623	0.0178	2.9418	0.3339	IR protective	329.
hsa-miR-326	MI0000808	CCUCUGGGCCUUCUCCAG	0.7853	0.0140	0.1356	0.0288	IR sensitizing	330.
hsa-miR-328	MI0000804	CUGGGCCUUCUGCCCUCCGU	0.8115	0.0068	0.2910	0.0496	IR sensitizing	331.
hsa-miR-329	MI0001726	AACACACUGGUUAACCUUUU	1.1717	0.0574	0.1373	0.0234	IR sensitizing	332.
hsa-miR-329	MI0001725	AACACACUGGUUAACCUUUU	0.9473	0.0378	0.2880	0.0215	IR sensitizing	333.
hsa-miR-33	MI0000091	GUGCAUUGUAGUUGCAUUGCA	0.6470	0.0034	0.4414	0.0691	IR sensitizing	334.
hsa-miR-330	MI0000803	GCAAAGCACACGGCCUGCAGAGA	0.9970	0.0112	1.1123	0.2400	-	335.
hsa-miR-330-5p	MI0000803	UCUCUGGGCCUGUCUUUAGGC	0.5071	0.0536	0.1645	0.0253	IR sensitizing	336.
hsa-miR-331	MI0000812	GCCCCUGGGCCUAUCCUAGAA	0.7634	0.0016	1.6484	0.0252	-	337.
hsa-miR-331-5p	MI0000812	CUAGGUAGGUCCAGGGAUCC	0.9467	0.0235	0.8258	0.0365	-	338.
hsa-miR-335	MI0000816	UCAAGAGCAAUAAAGAAAAAUGU	0.8764	0.0068	1.9688	0.1764	-	339.
hsa-miR-335*	MI0000816	UUUUUCAUUAUUGCUCCUGACC	0.7115	0.0192	0.1986	0.0168	IR sensitizing	340.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-337	MI0000806	CUCCUAUAUGAUGCCUUUCUUC	0.7345	0.0181	0.9585	0.1114	-	341.
hsa-miR-337-5p	MI0000806	GAACGGCUUCAUACAGGAGUU	0.8500	0.0075	0.7441	0.0795	-	342.
hsa-miR-338	MI0000814	UCCAGCAUCAGUGAUUUUGUUG	0.7133	0.0172	0.3240	0.0858	IR sensitizing	343.
hsa-miR-338-5p	MI0000814	AACAUAUCCUGGUGCUGAGUG	0.8295	0.0077	1.4913	0.0986	-	344.
hsa-miR-339	MI0000815	UCCCUGUCCUCCAGGAGCUCACG	0.8039	0.0098	0.4180	0.0150	IR sensitizing	345.
hsa-miR-339-3p	MI0000815	UGAGCGCCUCCGACGACAGAGCCG	0.4785	0.0148	0.2259	0.0177	Toxic	346.
hsa-miR-33a*	MI0000091	CAAUUUUUCCACAGUGCAUCAC	0.8404	0.0405	0.4117	0.0195	IR sensitizing	347.
hsa-miR-33b	MI0003646	GUGCAUUGCUGUUGCAUUGC	0.6425	0.0055	0.3032	0.0506	IR sensitizing	348.
hsa-miR-33b*	MI0003646	CAGUGCCUCCGCGAGUGCAGCCCC	0.9768	0.0080	1.7499	0.1021	-	349.
hsa-miR-340	MI0000802	UUUAAAGCAAUGAGACUGAUU	0.6925	0.0137	0.2293	0.0398	IR sensitizing	350.
hsa-miR-340*	MI0000802	UCCGUCACGUUACUUUAUAGC	0.6372	0.0056	0.1367	0.0135	IR sensitizing	351.
hsa-miR-342	MI0000805	UCUCACACAGAAAUCGACCCGU	0.7812	0.0182	1.6120	0.0474	-	352.
hsa-miR-342-5p	MI0000805	AGGGUGCUAUCUGUGAUUGA	0.0672	0.0024	0.1026	0.0143	Toxic	353.
hsa-miR-345	MI0000825	GCTUGACUCCUAGUCCAGGGCUC	1.0891	0.0598	5.5600	0.7885	IR protective	354.
hsa-miR-346	MI0000826	UGUCUGCCCGCAUGCCUGCCUCU	0.8484	0.0198	0.3433	0.0612	IR sensitizing	355.
hsa-miR-34a	MI0000268	UGGCAGUGUCUUAGCUGGUUGU	0.2667	0.0304	0.0891	0.0151	Toxic	356.
hsa-miR-34a*	MI0000268	CAAUCAGCAAGUAUCUGCCCU	0.7196	0.0242	0.0680	0.0147	IR sensitizing	357.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-34b	MI0000742	CAAUCACUAAUCCACUGCCAU	0.7942	0.0396	0.9920	0.1351	-	358.
hsa-miR-34b*	MI0000742	UAGGCAGUGUCAUAGCUGAUUG	0.1111	0.0293	0.0598	0.0018	Toxic	359.
hsa-miR-34c	MI0000743	AGGCAGUGUAGUAGCUGAUUGC	0.0338	0.0095	0.0307	0.0032	Toxic	360.
hsa-miR-34c-3p	MI0000743	AAUCACUAAACCACACGGCCAGG	0.8070	0.0194	1.1380	0.1890	-	361.
hsa-miR-361	MI0000760	UUAUAGAAUUCUCCAGGGGUAC	0.7235	0.0102	1.0170	0.0720	-	362.
hsa-miR-361-3p	MI0000760	UCCCCAGGUGUGAUUCUGAUUU	0.7810	0.0129	0.8089	0.0388	-	363.
hsa-miR-362	MI0000762	AAUCCUUGGAACCUAGGUGUGAGU	0.6802	0.0102	0.1091	0.0068	IR sensitizing	364.
hsa-miR-362-3p	MI0000762	AACACACCUAUUCAGGAUUA	0.5987	0.0031	0.1801	0.0171	IR sensitizing	365.
hsa-miR-363	MI0000764	AAUUGCACGGUAUCCAUCUGUA	1.0002	0.0246	1.7715	0.2485	-	366.
hsa-miR-363*	MI0000764	CGGGUGGAUCACGAUGCAAUUU	0.3956	0.1047	0.0545	0.0038	Toxic	367.
hsa-miR-365	MI0000769	UAAUGCCCCUAAAAAUCCUUAU	0.7540	0.0240	0.3213	0.0308	IR sensitizing	368.
hsa-miR-365	MI0000767	UAAUGCCCCUAAAAAUCCUUAU	0.7982	0.0457	0.3419	0.1037	IR sensitizing	369.
hsa-miR-367	MI0000775	AAUUGCACUUUAGCAAUGGUGA	0.7129	0.0064	1.2113	0.0143	-	370.
hsa-miR-367*	MI0000775	ACUGUUGCUAAUAUGCAACUCU	0.6380	0.0116	0.0889	0.0126	IR sensitizing	371.
hsa-miR-368	MI0000776	AACAUAGAGGAAAUUCCACGU	0.5459	0.0280	0.0483	0.0027	IR sensitizing	372.
hsa-miR-369-3p	MI0000777	AAUAAUACAUGGUUGAUUUUU	0.7892	0.0383	1.0753	0.0353	-	373.
hsa-miR-369-5p	MI0000777	AGAUCGACCGUGUUAUUAUUCGC	1.1424	0.0157	4.2064	0.0948	IR protective	374.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-370	MI0000778	GCCUGCUGGGGUGGAACCUGGU	0.6901	0.0086	0.7128	0.0607	-	375.
hsa-miR-371	MI0000779	AAGUGCCGCCAUCUUUUGAGUGU	0.5925	0.0202	0.2163	0.0220	IR sensitizing	376.
hsa-miR-371-5p	MI0000779	ACUCAAAACUGUGGGGGCACU	0.9237	0.0105	2.4737	0.6890	IR protective	377.
hsa-miR-372	MI0000780	AAAGUCUGCGACAUUUGAGCGU	0.8707	0.0241	0.5414	0.0194	-	378.
hsa-miR-373	MI0000781	GAAAGUCUUCGAUUUUGGGGUGU	0.7551	0.0391	0.4346	0.0055	IR sensitizing	379.
hsa-miR-373*	MI0000781	ACUCAAAUUGGGGGCGCUUCC	0.8890	0.0279	1.2388	0.0577	-	380.
hsa-miR-374	MI0000782	UUUAUUAUACAACCGUGAUAAAGUG	0.6917	0.0270	0.3513	0.0816	IR sensitizing	381.
hsa-miR-374a*	MI0000782	CUUAUCAGAUUGUAUUGUAAUU	0.8159	0.0139	2.0573	0.2078	IR protective	382.
hsa-miR-374b	MI0005566	AUAUAAUACAACCGUCUAAAGUG	0.7118	0.0143	0.1467	0.0135	IR sensitizing	383.
hsa-miR-374b*	MI0005566	CUUAGCAGGUUGUAUUAUCAUU	0.6648	0.0020	0.1282	0.0146	IR sensitizing	384.
hsa-miR-375	MI0000783	UUUGUUCGUUCGGCUCGCGUGA	0.6818	0.0055	0.2955	0.0176	IR sensitizing	385.
hsa-miR-376a	MI0000784	AUCAUAGAGGAAAAUCCACGU	0.6894	0.0300	0.1470	0.0282	IR sensitizing	386.
hsa-miR-376a	MI0003529	AUCAUAGAGGAAAAUCCACGU	0.7697	0.0222	0.1548	0.0217	IR sensitizing	387.
hsa-miR-376a*	MI0000784	GUAGAUAUCUCCUUAUGAGUA	0.6199	0.0031	0.2053	0.0311	IR sensitizing	388.
hsa-miR-376b	MI0002466	AUCAUAGAGGAAAAUCCAUUUU	0.6422	0.3699	0.5357	0.1057	-	389.
hsa-miR-377	MI0000785	AUCACACAAAGCAACUUUUUGU	0.7637	0.0350	0.6916	0.0255	-	390.
hsa-miR-377*	MI0000785	AGAGGUUGCCCUUGGUGAAUUC	0.4990	0.0197	0.1815	0.0261	Toxic	391.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-378	MI0000786	CUCCUGACUCCAGGUCCUGUGU	0.2682	0.0122	0.0673	0.0131	Toxic	392.
hsa-miR-379	MI0000787	UGGUAGACUAUGGAACGUAGG	0.7183	0.0142	0.2022	0.0107	IR sensitizing	393.
hsa-miR-379*	MI0000787	UAUGUAAACAUUGGUCCACUAAU	0.7812	0.0178	1.1058	0.1554	-	394.
hsa-miR-380-3p	MI0000788	UAUGUAAUUGGUCCACAUUU	0.7883	0.0064	0.2017	0.0162	IR sensitizing	395.
hsa-miR-380-5p	MI0000788	UGGUUGACCAUAGAACAUAGCG	0.4649	0.0134	0.0705	0.0061	Toxic	396.
hsa-miR-381	MI0000789	UAUACAAGGCAAGCUCUCUGU	1.0668	0.0135	3.2926	0.4336	IR protective	397.
hsa-miR-382	MI0000790	GAAGUUGUUCGUGGGAUUCG	0.8848	0.0124	0.5087	0.0527	-	398.
hsa-miR-383	MI0000791	AGAUCAAGGUGAUUUGGCU	0.9226	0.0053	0.1413	0.0182	IR sensitizing	399.
hsa-miR-384	MI0001145	AUUCUAGAAAUUUUCAUA	0.8937	0.0117	1.1252	0.1474	-	400.
hsa-miR-409-3p	MI0001735	GAAUGUUGCUCGGUGAACCCCU	0.8791	0.0288	0.7930	0.1774	-	401.
hsa-miR-409-5p	MI0001735	AGGUUACCCGAGCAACUUUGCAU	0.8874	0.0264	1.3323	0.2365	-	402.
hsa-miR-410	MI0002465	AAUUAACACAGAUUGGCCUGU	1.2396	0.0469	1.6677	0.1026	-	403.
hsa-miR-411	MI0003675	UAGUAGACCGUUAAGCGUACG	0.6810	0.0156	0.1714	0.0257	IR sensitizing	404.
hsa-miR-411*	MI0003675	UAUGUAAACACGGUCCACUAAAC	0.6897	0.0453	0.7192	0.0539	-	405.
hsa-miR-412	MI0002464	ACUUCACCUUGGUCCACUAGCCGU	1.1815	0.0210	3.2521	0.3003	IR protective	406.
hsa-miR-421	MI0003685	AUCAACAGACAUAAUUUGGCGC	0.6503	0.0206	0.1466	0.0044	IR sensitizing	407.
hsa-miR-422a	MI0001444	ACUGGACUAGGGUAGGAAGGC	0.7940	0.0321	0.2386	0.0391	IR sensitizing	408.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-422b	MI0000786	ACUGGACUUGGAGUCAGAAGG	0.6788	0.0410	0.4399	0.0297	IR sensitizing	409.
hsa-miR-423	MI0001445	AGCUCGGUCUGAGGCCCCUCAGU	0.6857	0.0423	0.3875	0.1104	IR sensitizing	410.
hsa-miR-423-5p	MI0001445	UGAGGGGCAGAGCGGAGACUUU	0.3975	0.0340	0.5479	0.0592	Toxic	411.
hsa-miR-424	MI0001446	CAGCAGCAAUUC AUGUUUGAA	0.2519	0.0209	0.1012	0.0055	Toxic	412.
hsa-miR-424*	MI0001446	CAAAACGUGAGGCGCUGCUAU	0.6483	0.0584	0.2811	0.0099	IR sensitizing	413.
hsa-miR-425	MI0001448	AUCGGGAUUGUCGUGCCGCC	0.8161	0.0175	0.6238	0.1147	-	414.
hsa-miR-425-5p	MI0001448	AAUGACACGAUCUCCCCGUUGA	0.3544	0.0023	0.1502	0.0035	Toxic	415.
hsa-miR-429	MI0001641	UAAUACUGUCUGGUAACCGU	0.8327	0.0057	1.9271	0.0480	-	416.
hsa-miR-431	MI0001721	UGUCUUGCAGGCCGUC AUGCA	1.0240	0.0292	0.3906	0.0182	IR sensitizing	417.
hsa-miR-431*	MI0001721	CAGGUCGUCUUGCAGGCUUCU	0.7000	0.0064	0.3120	0.0525	IR sensitizing	418.
hsa-miR-432	MI0003133	UCUUGGAGUAGGUC AUUGGGUGG	0.5607	0.3146	0.4984	0.1154	IR sensitizing	419.
hsa-miR-432*	MI0003133	CUGGAUGGCUCCUCC AUGUCU	1.0524	0.0072	3.8939	0.0797	IR protective	420.
hsa-miR-433	MI0001723	AUCAUGAUGGGCUCCUGGUGU	0.9573	0.0150	1.5129	0.0896	-	421.
hsa-miR-448	MI0001637	UUGCAUAUGUAGGAUGUCCCAU	0.9678	0.0083	0.1416	0.0112	IR sensitizing	422.
hsa-miR-449	MI0001648	UGGCAGUGUAUUGUAGCUGGU	0.1028	0.0304	0.0498	0.0017	Toxic	423.
hsa-miR-449b	MI0003673	AGGCAGUGUAUUGUAGCUGGC	0.0405	0.0070	0.0445	0.0015	Toxic	424.
hsa-miR-450	MI0003187	UUUUGCGAUGUGUCCUAAUUAU	0.7110	0.0074	0.8752	0.1543	-	425.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-450	MI0001652	UUUUGCGAUGUUGCUAAUUAU	0.6683	0.0098	0.9284	0.1444	-	426.
hsa-miR-450b-3p	MI0005531	UUGGGAUCAUUUGCAUCCAUA	0.8059	0.0354	0.1829	0.0111	IR sensitizing	427.
hsa-miR-450b-5p	MI0005531	UUUUGCAAUAUUGUCCUGAAUA	0.8114	0.0487	0.5723	0.0655	-	428.
hsa-miR-451	MI0001729	AAACCGUUAACCAUACUGAGUU	0.9698	0.0437	1.4441	0.0927	-	429.
hsa-miR-452	MI0001733	AACUGUUUGCAGAGAAACUGA	0.7812	0.0112	0.8885	0.0764	-	430.
hsa-miR-452*	MI0001733	CUCAUCUGCAAAGAAGUAAGUG	0.8246	0.0076	0.1723	0.0201	IR sensitizing	431.
hsa-miR-453	MI0001727	AGGUUGUCCGUGGUGAGUUCGCA	0.6259	0.0588	0.1360	0.0214	IR sensitizing	432.
hsa-miR-454-3p	MI0003820	UAGUGCAAUAUUGCUUAUAGGGU	0.8097	0.0045	0.2775	0.0278	IR sensitizing	433.
hsa-miR-454-5p	MI0003820	ACCCUAUCAAUAUUGUCUCUCG	0.8259	0.0062	0.5963	0.0183	-	434.
hsa-miR-455	MI0003513	UAUGUGCCUUUGGACUACAUCG	0.9443	0.0050	2.2518	0.0449	IR protective	435.
hsa-miR-455-3p	MI0003513	GCAGUCCAUGGGCAUAUACAC	0.8003	0.0092	1.8879	0.3174	-	436.
hsa-miR-483	MI0002467	UCACUCCUCUCCUCCCGUCUU	0.9341	0.0249	0.9446	0.2358	-	437.
hsa-miR-483-5p	MI0002467	AAGACGGGAGGAAAGAAGGGAG	0.6595	0.0196	0.4892	0.0409	IR sensitizing	438.
hsa-miR-484	MI0002468	UCAGGCUCAGUCCUCCUCCCGAU	1.1001	0.0187	1.1478	0.1968	-	439.
hsa-miR-485-3p	MI0002469	GUCAUACACGGCUCUCCUCUCU	1.0957	0.0099	0.7378	0.0493	-	440.
hsa-miR-485-5p	MI0002469	AGAGGCUGCCCGUGAU'GAAUUC	0.5343	0.0401	0.1239	0.0056	IR sensitizing	441.
hsa-miR-486	MI0002470	UCCUGUACUGAGCUGCCCCGAG	1.0456	0.0204	1.5817	0.0471	-	442.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-486-3p	MI0002470	CGGGGCAGCUCAGUACAGGAU	0.6170	0.0117	0.0967	0.0081	IR sensitizing	443.
hsa-miR-487	MI0002471	AAUCAUACAGGGACAUCCAGUU	0.8891	0.0194	0.6297	0.0457	-	444.
hsa-miR-487b	MI0003530	AAUCGUACAGGGUACUCCACUU	0.8524	0.0117	0.2625	0.0465	IR sensitizing	445.
hsa-miR-488	MI0003123	UUGAAAGGCUAUUUCUUGGUC	0.6810	0.0173	0.1839	0.0142	IR sensitizing	446.
hsa-miR-488*	MI0003123	CCCAGAUAAUGGCACUCUCAA	0.5267	0.0432	0.0947	0.0084	IR sensitizing	447.
hsa-miR-489	MI0003124	GUGACAUCACAUACGGGCAGC	0.2339	0.0336	0.0664	0.0034	Toxic	448.
hsa-miR-490	MI0003125	CAACCUGGAGGACUCCAUUGCUG	0.8370	0.0103	0.5056	0.0296	-	449.
hsa-miR-490-5p	MI0003125	CCAUGGAUCCAGGUGGGU	0.6066	0.0120	0.4238	0.0247	IR sensitizing	450.
hsa-miR-491	MI0003126	AGUGGGGAACCCUCCAUAGAGG	0.6690	0.0282	0.1739	0.0428	IR sensitizing	451.
hsa-miR-491-3p	MI0003126	CUUAUGCAAAGAUUCCUUCUAC	0.8107	0.0241	0.3172	0.0155	IR sensitizing	452.
hsa-miR-492	MI0003131	AGGACCUGCCGGACAAAGAUUCUU	0.8874	0.0186	0.5068	0.0741	-	453.
hsa-miR-493	MI0003132	UUGUACAUGGUAGGCUUUCUAUU	0.6948	0.0501	0.1850	0.0174	IR sensitizing	454.
hsa-miR-493-3p	MI0003132	UGAAGGUCUACUGUGGCCAGG	0.8973	0.0211	1.1629	0.1847	-	455.
hsa-miR-494	MI0003134	UGAAACAUAACACGGGAAACCUC	0.7433	0.0125	0.2947	0.0755	IR sensitizing	456.
hsa-miR-495	MI0003135	AAACAACAUGGUGCAUUCUU	0.8821	0.0174	4.2017	0.5922	IR protective	457.
hsa-miR-496	MI0003136	UGAGUAUUACAUGGCCAAUCUC	0.6654	0.0318	0.2846	0.0470	IR sensitizing	458.
hsa-miR-497	MI0003138	CAGCAGCACACUGGUGUUUGU	0.1585	0.0151	0.0746	0.0033	Toxic	459.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-497*	MI0003138	CAAACCACACUGUGGUUAGA	0.7026	0.0210	0.5060	0.0582	-	460.
hsa-miR-498	MI0003142	UUUCAAGCCAGGGGCGUUUUC	0.7432	0.0210	0.3820	0.0170	IR sensitizing	461.
hsa-miR-499	MI0003183	UUAAGACUUGCAGUGAUUUU	0.7906	0.0112	0.3561	0.0627	IR sensitizing	462.
hsa-miR-499-3p	MI0003183	AACAUCACAGCAAGUCUGUCU	0.4860	0.0443	0.0907	0.0072	Toxic	463.
hsa-miR-500	MI0003184	UAAUCCUUGCUACCGGGGUGAGA	0.7435	0.0011	0.4037	0.0077	IR sensitizing	464.
hsa-miR-500*	MI0003184	AUGCACCUGGGCAAGGAUUCUG	0.8974	0.0163	0.7622	0.0465	-	465.
hsa-miR-501	MI0003185	AAUCCUUUGUCCCGGGUGAGA	0.9441	0.0094	2.3920	0.0912	IR protective	466.
hsa-miR-501-3p	MI0003185	AAUGCACCCGGGCAAGGAUUCU	0.7725	0.0093	0.4388	0.0085	IR sensitizing	467.
hsa-miR-502	MI0003186	AUCCUUGCUAUCUGGGGUGCUA	0.9502	0.0164	2.5154	0.0730	IR protective	468.
hsa-miR-502-3p	MI0003186	AAUGCACCUGGGCAAGGAUUCU	0.6584	0.0301	0.1901	0.0122	IR sensitizing	469.
hsa-miR-503	MI0003188	UAGCAGCGGGAACAGUUCUGCAG	0.9832	0.0119	2.4523	0.0649	IR protective	470.
hsa-miR-504	MI0003189	AGACCCUGGUCUGCACUCUAUC	1.0856	0.0029	1.6433	0.3473	-	471.
hsa-miR-505	MI0003190	CGUCAACACUUGCUGGUUUCCU	0.8878	0.0095	0.8676	0.0373	-	472.
hsa-miR-505*	MI0003190	GGGAGCCAGGAAGAUUUGAUGU	0.8983	0.0079	0.2728	0.0321	IR sensitizing	473.
hsa-miR-506	MI0003193	UAAGGCACCCUUCUGAGUAGA	0.5543	0.0333	0.0803	0.0045	IR sensitizing	474.
hsa-miR-507	MI0003194	UUUUGCACCUUUUGGAGUGAA	0.7825	0.0055	0.3769	0.0166	IR sensitizing	475.
hsa-miR-508	MI0003195	UGAUUGUAGCCUUUUGGAGUAGA	0.8740	0.0057	1.4288	0.1845	-	476.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-508-5p	MI0003195	UACUCCAGAGGGCGUCACUCAUG	0.7548	0.0074	0.4269	0.0123	IR sensitizing	477.
hsa-miR-509	MI0003196	UGAUUGGUACGUCUGUGGGUAG	0.6686	0.0364	0.1631	0.0229	IR sensitizing	478.
hsa-miR-509-3-5p	MI0005717	UACUGCAGACGUGGCAAUCAUG	0.3154	0.0213	0.0711	0.0047	Toxic	479.
hsa-miR-509-3p	MI0005530	UGAUUGGUACGUCUGUGGGUAG	0.6987	0.0088	0.0829	0.0072	IR sensitizing	480.
hsa-miR-509-3p	MI0005717	UGAUUGGUACGUCUGUGGGUAG	0.4994	0.0241	0.0912	0.0139	Toxic	481.
hsa-miR-509-5p	MI0003196	UACUGCAGACAGUGGCAAUCA	0.6565	0.0099	0.1109	0.0049	IR sensitizing	482.
hsa-miR-509-5p	MI0005530	UACUGCAGACAGUGGCAAUCA	0.6132	0.0135	0.2031	0.0241	IR sensitizing	483.
hsa-miR-510	MI0003197	UACUCAGGAGAGUGGCAAUAC	0.3797	0.0141	0.0941	0.0279	Toxic	484.
hsa-miR-511	MI0003128	GUGUCUUUUGCUCUCAGUCA	0.8739	0.0117	0.5457	0.0225	-	485.
hsa-miR-511	MI0003127	GUGUCUUUUGCUCUCAGUCA	1.0914	0.0120	2.8442	0.1821	IR protective	486.
hsa-miR-512-3p	MI0003140	AAGUCUGUCAUAGCUGAGGUC	0.8856	0.0061	0.6092	0.0360	-	487.
hsa-miR-512-3p	MI0003141	AAGUCUGUCAUAGCUGAGGUC	0.8972	0.0110	0.6399	0.0279	-	488.
hsa-miR-512-5p	MI0003141	CACUCAGCCUUGAGGGCACUUUC	1.0416	0.0055	3.3262	0.1569	IR protective	489.
hsa-miR-512-5p	MI0003140	CACUCAGCCUUGAGGGCACUUUC	0.5616	0.0650	0.1510	0.0048	IR sensitizing	490.
hsa-miR-513	MI0003191	UUCACAGGGAGGUGUCAU	0.8605	0.0186	0.5410	0.1058	-	491.
hsa-miR-513	MI0003192	UUCACAGGGAGGUGUCAU	0.7976	0.0375	0.8446	0.1911	-	492.
hsa-miR-513a-3p	MI0003192	UAAAUUUCACCUUUCUGAGAAGG	0.5170	0.0117	0.0816	0.0023	IR sensitizing	493.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-513a-3p	MI0003191	UAAUUUCACCUUUCUGAGAAGG	0.6303	0.0384	0.1115	0.0187	IR sensitizing	494.
hsa-miR-513b	MI0006648	UUCACAAAGGAGGUGUCAUUUAU	0.9137	0.0137	1.7566	0.0194	-	495.
hsa-miR-513c	MI0006649	UUCUCAAGGAGGUGUGUUUAU	1.0313	0.0723	0.4095	0.0132	IR sensitizing	496.
hsa-miR-514	MI0003199	AUUGACACUUCUGUGAGUAGA	0.7565	0.0036	1.6949	0.2566	-	497.
hsa-miR-514	MI0003200	AUUGACACUUCUGUGAGUAGA	0.7103	0.0119	2.4265	0.3499	IR protective	498.
hsa-miR-514	MI0003198	AUUGACACUUCUGUGAGUAGA	0.8253	0.0087	3.7086	0.5119	IR protective	499.
hsa-miR-515-3p	MI0003147	GAGUGCCUUCUUUUGGAGCGUU	0.7779	0.0138	0.5092	0.0793	-	500.
hsa-miR-515-3p	MI0003144	GAGUGCCUUCUUUUGGAGCGUU	0.7533	0.0073	0.6548	0.1033	-	501.
hsa-miR-515-5p	MI0003147	UUCUCCAAAAGAAAGCACUUUCUG	0.5560	0.3078	0.9750	0.0343	-	502.
hsa-miR-515-5p	MI0003144	UUCUCCAAAAGAAAGCACUUUCUG	0.8860	0.0181	0.4687	0.1195	IR sensitizing	503.
hsa-miR-516-3p	MI0003180	UGC UUCUUUCAGAGGGU	0.8932	0.0036	0.6242	0.0528	-	504.
hsa-miR-516-3p	MI0003172	UGC UUCUUUCAGAGGGU	0.5669	0.3135	2.5551	0.1291	IR protective	505.
hsa-miR-516-3p	MI0003167	UGC UUCUUUCAGAGGGU	0.8529	0.0210	0.2033	0.0126	IR sensitizing	506.
hsa-miR-516-3p	MI0003181	UGC UUCUUUCAGAGGGU	0.6805	0.0713	0.2239	0.0069	IR sensitizing	507.
hsa-miR-516-5p	MI0003172	AUCUGGAGGUAAGAAAGCACUUU	0.2144	0.0145	0.1426	0.0253	Toxic	508.
hsa-miR-516-5p	MI0003167	AUCUGGAGGUAAGAAAGCACUUU	0.3409	0.0538	0.1123	0.0218	Toxic	509.
hsa-miR-516a-5p	MI0003180	UUCUCGAGGAAAAGAACUUUC	0.7827	0.0085	0.8819	0.2022	-	510.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-516a-5p	MI0003181	UUCUCGAGGAAAGACACUUUC	0.7006	0.0074	0.3516	0.0708	IR sensitizing	511.
hsa-miR-517*	MI0003165	CCUCUAGAUGGAAAGCACUGUCU	0.9449	0.0156	0.7267	0.1038	-	512.
hsa-miR-517*	MI0003174	CCUCUAGAUGGAAAGCACUGUCU	0.9309	0.0248	0.8625	0.0561	-	513.
hsa-miR-517*	MI0003161	CCUCUAGAUGGAAAGCACUGUCU	0.9436	0.0104	1.0990	0.0562	-	514.
hsa-miR-517a	MI0003161	AUCGUGCAUCCCUUUAGAGUGU	0.7709	0.0488	0.3399	0.0559	IR sensitizing	515.
hsa-miR-517b	MI0003165	UCGUGCAUCCCUUUAGAGUGU	0.9737	0.0309	0.1876	0.0104	IR sensitizing	516.
hsa-miR-517c	MI0003174	AUCGUGCAUCCCUUUAGAGUGU	0.6778	0.0619	0.1651	0.0137	IR sensitizing	517.
hsa-miR-518a	MI0003173	GAAAGCGCUUCCCUUUGCUGGA	0.5982	0.0336	0.2504	0.0507	IR sensitizing	518.
hsa-miR-518a	MI0003170	GAAAGCGCUUCCCUUUGCUGGA	0.6013	0.0220	0.4107	0.0840	IR sensitizing	519.
hsa-miR-518a-5p	MI0003170	CUGCAAAGGGAAGCCCUUUC	0.1745	0.0173	0.1342	0.0146	Toxic	520.
hsa-miR-518a-5p	MI0003173	CUGCAAAGGGAAGCCCUUUC	0.2110	0.0103	0.1465	0.0210	Toxic	521.
hsa-miR-518b	MI0003156	CAAAGCGCUUCCCUUUAGAGGU	0.5793	0.0042	0.1397	0.0149	IR sensitizing	522.
hsa-miR-518c	MI0003159	CAAAGCGCUUCCCUUUAGAGUGU	0.6253	0.0183	0.4060	0.0622	IR sensitizing	523.
hsa-miR-518c*	MI0003159	UCUCUGGAGGGAAGCACUUUCUG	0.9459	0.0129	0.3840	0.0260	IR sensitizing	524.
hsa-miR-518d	MI0003171	CAAAGCGCUUCCCUUUGGAGC	0.5266	0.0046	0.1583	0.0073	IR sensitizing	525.
hsa-miR-518d-5p	MI0003171	CUCUAGAGGGAAGCACUUUCUG	0.8675	0.0075	1.3506	0.2692	-	526.
hsa-miR-518e	MI0003169	AAAGCGCUUCCCUUCAGAGUG	0.7421	0.0067	0.7594	0.1167	-	527.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-518e*	MI0003169	CUCUAGAGGGGAAGCGCUUUCUG	0.8026	0.0229	0.9902	0.2155	-	528.
hsa-miR-518f	MI0003154	GAAAGCGCUUCUCUUUAGAGG	0.7276	0.0270	1.2259	0.1963	-	529.
hsa-miR-518f*	MI0003154	CUCUAGAGGGGAAGCACUUUCUC	0.8940	0.0024	1.2722	0.1915	-	530.
hsa-miR-519a	MI0003178	AAAGUGCAUCCUUUUAGAGUGU	0.8310	0.0043	0.8045	0.1187	-	531.
hsa-miR-519a	MI0003182	AAAGUGCAUCCUUUUAGAGUGU	0.9624	0.0040	1.2077	0.1815	-	532.
hsa-miR-519a*	MI0003178	CUCUAGAGGGGAAGCGCUUUCUG	0.7510	0.0092	0.7342	0.0275	-	533.
hsa-miR-519b	MI0003151	AAAGUGCAUCCUUUUAGAGGUU	0.9189	0.0113	0.7252	0.1405	-	534.
hsa-miR-519b-5p	MI0003151	CUCUAGAGGGGAAGCGCUUUCUG	0.7920	0.0042	0.9310	0.0826	-	535.
hsa-miR-519c	MI0003148	AAAGUGCAUCCUUUUAGAGGAU	0.9693	0.0130	0.5905	0.0473	-	536.
hsa-miR-519d	MI0003162	CAAAGUGCCUCCUUUAGAGUG	0.8220	0.0202	2.0405	0.3401	IR protective	537.
hsa-miR-519e	MI0003145	AAGUGCCUCCUUUUAGAGUGU	0.6499	0.0062	0.3304	0.0517	IR sensitizing	538.
hsa-miR-519e*	MI0003145	UUCUCCAAAAGGAGCACUUUC	0.8457	0.0089	0.3640	0.0469	IR sensitizing	539.
hsa-miR-520a	MI0003149	AAAGUGCUUCCUUUGGACUGU	0.8745	0.0012	0.7234	0.0544	-	540.
hsa-miR-520a*	MI0003149	CUCCAGAGGGAAGUACUUUCU	0.7696	0.0110	0.4450	0.0159	IR sensitizing	541.
hsa-miR-520b	MI0003155	AAAGUGCUUCCUUUUAGAGGG	0.8910	0.0112	0.8880	0.0533	-	542.
hsa-miR-520c	MI0003158	AAAGUGCUUCCUUUUAGAGGGU	0.7876	0.0048	0.9885	0.1667	-	543.
hsa-miR-520c-5p	MI0003158	CUCUAGAGGGGAAGCACUUUCUG	0.8440	0.0019	1.4779	0.0571	-	544.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-520d	MI0003164	AAAGUGCUUCUUCUUGGUGGGU	0.9032	0.0444	1.2926	0.1928	—	545.
hsa-miR-520d*	MI0003164	CUACAAAGGGAAGCCCUUUC	0.7608	0.0240	0.1496	0.0244	IR sensitizing	546.
hsa-miR-520e	MI0003143	AAAGUCUUCUUCUUUUGAGGG	0.9157	0.0439	0.6997	0.0412	—	547.
hsa-miR-520f	MI0003146	AAGUCUUCUUCUUUAGAGGGUU	0.8903	0.0068	0.6164	0.0233	—	548.
hsa-miR-520g	MI0003166	ACAAAGUCUUCUCCUUUAGAGUGU	0.9687	0.0017	1.3169	0.0865	—	549.
hsa-miR-520h	MI0003175	ACAAAGUCUUCUCCUUUAGAGU	0.9646	0.0093	1.6814	0.0516	—	550.
hsa-miR-521	MI0003163	AACGCACUUCUCCUUUAGAGUGU	0.7223	0.0267	0.2880	0.0129	IR sensitizing	551.
hsa-miR-521	MI0003176	AACGCACUUCUCCUUUAGAGUGU	0.7187	0.0149	0.2977	0.0275	IR sensitizing	552.
hsa-miR-522	MI0003177	AAAAUGGUUCCUUCUUUAGAGUGU	0.0629	0.0050	0.0537	0.0088	Toxic	553.
hsa-miR-522*	MI0003177	CUCUAGAGGGAAGCGCUUUCUG	0.7823	0.0121	0.8822	0.0178	—	554.
hsa-miR-523	MI0003153	GAACGGCUUCUCCUUAUAGAGGGU	0.9401	0.0230	3.4475	0.4857	IR protective	555.
hsa-miR-523*	MI0003153	CUCUAGAGGGAAGCGCUUUCUG	0.7568	0.0188	1.2392	0.0438	—	556.
hsa-miR-524	MI0003160	GAAGGCGUUCUCCUUUGGAGU	0.8323	0.0173	0.4250	0.0094	IR sensitizing	557.
hsa-miR-524*	MI0003160	CUACAAAGGGAAGCACUUUCUC	0.4239	0.2354	0.0898	0.0023	Toxic	558.
hsa-miR-525	MI0003152	CUCCAGAGGGAUCCACUUUCU	0.6866	0.0198	0.2732	0.0258	IR sensitizing	559.
hsa-miR-525*	MI0003152	GAAGGCGUUCUCCUUUAGAGCG	0.8352	0.0156	0.7248	0.1128	—	560.
hsa-miR-526a	MI0003157	CUCUAGAGGGAAGCACUUUCUG	0.8959	0.0102	1.8187	0.2582	—	561.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-526a	MI0003168	CUCUAGAGGGAAAGCACUUUCUG	0.8567	0.0041	2.2646	0.3387	IR protective	562.
hsa-miR-526b	MI0003150	CUCUUGAGGGAAAGCACUUUCUGU	0.6406	0.0145	0.1201	0.0204	IR sensitizing	563.
hsa-miR-526b*	MI0003150	GAAAGUGCUUCCUUUUAGAGGC	0.8523	0.0155	1.8542	0.2576	—	564.
hsa-miR-526c	MI0003148	CUCUAGAGGGAAAGCGCUUUCUG	0.8395	0.0103	1.0275	0.1531	—	565.
hsa-miR-527	MI0003179	CUGCAAAGGGAAGCCUUUC	0.3343	0.0352	0.1093	0.0217	Toxic	566.
hsa-miR-532	MI0003205	CAUGCCUUGAGUGUAGGACCGU	0.6707	0.0056	0.0927	0.0076	IR sensitizing	567.
hsa-miR-532-3p	MI0003205	CCUCCACACCCAAAGCUUGCA	0.7441	0.0181	0.7944	0.0212	—	568.
hsa-miR-539	MI0003514	GGAGAAUUAUCCUUGGUGUGU	0.9824	0.0172	1.5754	0.2226	—	569.
hsa-miR-541	MI0005539	UGGUGGACACAGAAUCUGGACU	0.1194	0.0365	0.0337	0.0025	Toxic	570.
hsa-miR-541*	MI0005539	AAAGGAUUCUGCUGCGGUCCCACU	0.8635	0.0169	0.7416	0.0837	—	571.
hsa-miR-542-3p	MI0003686	UGUGACAGAUUGAUAAACUGAAA	0.7193	0.0082	0.1917	0.0233	IR sensitizing	572.
hsa-miR-542-5p	MI0003686	UCGGGGAUCAUCAUGUCACGAGA	0.7996	0.0166	0.7941	0.1062	—	573.
hsa-miR-543	MI0005565	AAACAUCGCGGUGCACUUCUU	0.8208	0.0275	0.7029	0.0050	—	574.
hsa-miR-544	MI0003515	AUUCUGCAUUUUUAGCAAGUUC	0.3391	0.0519	0.0860	0.0209	Toxic	575.
hsa-miR-545	MI0003516	UCAGCAAACAUAUUUUGUGUGC	0.8838	0.0154	1.5556	0.0835	—	576.
hsa-miR-545*	MI0003516	UCAGUAAAUUUUAUUAUGAUGA	0.8398	0.0070	1.7916	0.1651	—	577.
hsa-miR-548a	MI0003612	CAAAACUGGCAAUUACUUUUUGC	0.5615	0.0246	0.1504	0.0409	IR sensitizing	578.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-548a	MI0003598	CAAAACUGGCAAUACUUUUGC	0.7331	0.0052	0.2362	0.0290	IR sensitizing	579.
hsa-miR-548a	MI0003593	CAAAACUGGCAAUACUUUUGC	0.9207	0.0168	0.2621	0.0571	IR sensitizing	580.
hsa-miR-548a-5p	MI0003612	AAAAGUAAUUGCGAGUUUUACC	0.8131	0.0236	3.0684	0.3806	IR protective	581.
hsa-miR-548b	MI0003596	CAAGAACCUCAGUUCUUUUGU	0.8633	0.0147	2.5990	0.2763	IR protective	582.
hsa-miR-548b-5p	MI0003596	AAAAGUAAUUGUGUUUUUGGCC	0.7502	0.0191	1.3305	0.2143	—	583.
hsa-miR-548c	MI0003630	CAAAAUCUCAAUACUUUUGC	0.7667	0.0076	1.9333	0.2176	—	584.
hsa-miR-548c-5p	MI0003630	AAAAGUAAUUGCGUUUUUGCC	0.7914	0.0063	2.9747	0.6421	IR protective	585.
hsa-miR-548d	MI0003668	CAAAAACCACAGUUUCUUUUGC	0.8520	0.0036	0.5751	0.0556	—	586.
hsa-miR-548d	MI0003671	CAAAAACCACAGUUUCUUUUGC	0.7955	0.0054	0.9400	0.0139	—	587.
hsa-miR-548d-5p	MI0003671	AAAAGUAAUUGUGUUUUUGCC	0.9354	0.0061	4.9504	0.7523	IR protective	588.
hsa-miR-548d-5p	MI0003668	AAAAGUAAUUGUGUUUUUGCC	0.9215	0.0113	5.3036	0.3361	IR protective	589.
hsa-miR-549	MI0003679	UGACAACUUAUGGAUGAGCUCU	0.8640	0.0312	1.2823	0.0319	—	590.
hsa-miR-550	MI0003600	AGUGCCUGAGGAGUAAGAGCCC	0.6743	0.0180	0.6896	0.0635	—	591.
hsa-miR-550	MI0003601	AGUGCCUGAGGAGUAAGAGCCC	0.7218	0.0446	0.8664	0.0597	—	592.
hsa-miR-550	MI0003601	UGUCUUACUCCUCAGGCACAU	0.6330	0.0177	0.3177	0.0879	IR sensitizing	593.
hsa-miR-550	MI0003600	UGUCUUACUCCUCAGGCACAU	0.6664	0.0163	0.3968	0.0551	IR sensitizing	594.
hsa-miR-551a	MI0003556	GCGACCCACUUGGUUUCCA	0.5545	0.3069	1.2156	0.0853	—	595.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-551b	MI0003575	GCGACCCAUACUUGGUUUCAG	1.1278	0.0089	4.0334	0.1548	IR protective	596.
hsa-miR-551b*	MI0003575	GAAAUCAAGCGUGGGUGAGACC	0.8042	0.0185	1.9005	0.1411	—	597.
hsa-miR-552	MI0003557	AACAGGUGACUGGUUAGACAA	0.4642	0.0147	0.0714	0.0055	Toxic	598.
hsa-miR-553	MI0003558	AAAACGGUGAGAUUUUGUUUU	0.8194	0.0175	1.5763	0.0577	—	599.
hsa-miR-554	MI0003559	GCUAGUCCUGACUCAGCCAGU	0.9186	0.0031	1.2594	0.0934	—	600.
hsa-miR-555	MI0003561	AGGUUAGCUGAACCCUCUGAU	0.1162	0.0134	0.0879	0.0076	Toxic	601.
hsa-miR-556	MI0003562	GAUGAGCUCAUUGUAAU/AUGAG	0.8197	0.0145	1.7974	0.3142	—	602.
hsa-miR-556-3p	MI0003562	AUAUUACCAUUAAGCUCAUUUU	0.7398	0.0212	0.3305	0.0264	IR sensitizing	603.
hsa-miR-557	MI0003563	GUUUGCACGGGUGGGCCUUGUCU	0.7399	0.0086	0.4110	0.0303	IR sensitizing	604.
hsa-miR-558	MI0003564	UGAGCUGCUGUACCAAAU	0.6841	0.0507	0.1866	0.0166	IR sensitizing	605.
hsa-miR-559	MI0003565	UAAAGUAAAUUGCACCAAAA	0.9235	0.0211	1.9453	0.2155	—	606.
hsa-miR-561	MI0003567	CAAAGUUUAAGAUCUUGAAGU	0.8133	0.0008	0.2874	0.1278	IR sensitizing	607.
hsa-miR-562	MI0003568	AAAGUAGCUGUACCAUUUGC	0.6971	0.0215	0.1619	0.0192	IR sensitizing	608.
hsa-miR-563	MI0003569	AGGUUGACAUACGUUUCUCC	0.3863	0.2158	0.0908	0.0027	Toxic	609.
hsa-miR-564	MI0003570	AGGCACGGUGUACGAGGC	0.8192	0.0116	0.2706	0.0227	IR sensitizing	610.
hsa-miR-566	MI0003572	GGGCGCCUGUGAUCCCAAC	1.0821	0.0056	2.8244	0.2211	IR protective	611.
hsa-miR-567	MI0003573	AGUAUGUUCUUCAGGACAGAAC	0.8262	0.0014	0.3297	0.0680	IR sensitizing	612.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-568	MI0003574	AUGUAUAAUUAUACACAC	0.9697	0.0101	3.1237	0.2010	IR protective	613.
hsa-miR-569	MI0003576	AGUUAUAGAAUCCUGGAAAGU	1.0259	0.0196	1.8841	0.3260	-	614.
hsa-miR-570	MI0003577	CGAAAACAGCAAUACCUUUGC	0.8139	0.0214	0.3634	0.0646	IR sensitizing	615.
hsa-miR-571	MI0003578	UGAGUUGGCCAUCUGAGUGAG	0.5747	0.0629	0.1215	0.0034	IR sensitizing	616.
hsa-miR-572	MI0003579	GUCCGUCGCGGUGGCCCA	0.9886	0.0078	1.9423	0.1689	-	617.
hsa-miR-573	MI0003580	CUGAAGUGAUGUGUAACUGAUCAG	0.9939	0.0322	0.7947	0.0439	-	618.
hsa-miR-574	MI0003581	CACGCUCAUGCACACACCCACA	0.8017	0.0360	0.6905	0.1058	-	619.
hsa-miR-574-5p	MI0003581	UGAGUGUGUGUGUGAGUGUGU	0.6811	0.0222	0.4920	0.0911	IR sensitizing	620.
hsa-miR-575	MI0003582	GAGCCAGUUGGACAGGAGC	0.6206	0.3550	0.6197	0.0790	-	621.
hsa-miR-576	MI0003583	AUUCUAAUUUCCACGUCUUU	0.7617	0.0037	1.4493	0.2346	-	622.
hsa-miR-576-3p	MI0003583	AAGAUGUGGAAAAAUUGGAAUC	0.2807	0.0166	0.1449	0.0236	Toxic	623.
hsa-miR-577	MI0003584	UAGAUAAAUAUUGGUACCUG	1.0014	0.0250	4.8169	0.7454	IR protective	624.
hsa-miR-578	MI0003585	CUUCUUGUCUCUAGGAUUGU	0.8284	0.0423	0.0951	0.0195	IR sensitizing	625.
hsa-miR-579	MI0003586	UUCAUUUUGUAUAAACCGCGAUU	0.7297	0.0094	0.1653	0.0401	IR sensitizing	626.
hsa-miR-580	MI0003587	UUGAGAAUGAUGAAUUAUAGG	0.8543	0.0113	1.0707	0.1375	-	627.
hsa-miR-581	MI0003588	UCUUGUGUUCUCUAGAUCAGU	0.8913	0.0332	1.2881	0.3055	-	628.
hsa-miR-582	MI0003589	UUACAGUUGUUAACAGUUACU	0.8277	0.0316	1.1894	0.1452	-	629.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-582-3p	MI0003589	UAAUCUGGUUGAACAAACUGAACC	0.6629	0.0258	0.2721	0.0631	IR sensitizing	630.
hsa-miR-583	MI0003590	CAAAGAGGAAGGUCCCAUUAAC	0.8020	0.0215	0.3255	0.0267	IR sensitizing	631.
hsa-miR-584	MI0003591	UUAUGGUUUUGCCUGGACUGAG	0.9960	0.0202	0.6305	0.1587	-	632.
hsa-miR-585	MI0003592	UGGGCGUAUCUGUAUGCUA	0.6730	0.0421	0.0649	0.0256	IR sensitizing	633.
hsa-miR-586	MI0003594	UAUGCAUUGUAUUUUAGGUCC	0.8685	0.0187	1.2299	0.1391	-	634.
hsa-miR-587	MI0003595	UUUCCAUAGGUAGUAGUCAC	0.8276	0.0284	2.6334	0.1851	IR protective	635.
hsa-miR-588	MI0003597	UUGGCCACAAUGGGUUAAGAAC	0.5124	0.0164	0.2784	0.0566	IR sensitizing	636.
hsa-miR-589	MI0003599	UGAGAACCACGUCUCUCUGAG	0.6504	0.0510	0.4088	0.0425	IR sensitizing	637.
hsa-miR-589*	MI0003599	UCAGAACAAAUGCCGGUUCGCCAGA	0.9437	0.0105	1.2291	0.1367	-	638.
hsa-miR-590	MI0003602	GAGCUUAUUAUAAAGUAGCAG	0.7327	0.0198	1.0797	0.0457	-	639.
hsa-miR-590-3p	MI0003602	UAAUUUAUGUAUAAGCUAGU	0.7241	0.0287	0.8250	0.0788	-	640.
hsa-miR-591	MI0003603	AGACCAUGGGUUCUCAUUGU	0.6342	0.0056	0.3093	0.0671	IR sensitizing	641.
hsa-miR-592	MI0003604	UUGUGUCAUAUUGCGAUGAUGU	0.8591	0.0113	0.9833	0.2716	-	642.
hsa-miR-593	MI0003605	UGUCUCUCUGGGGUUUUCU	0.5897	0.0218	0.1131	0.0270	IR sensitizing	643.
hsa-miR-593*	MI0003605	AGGCACCAGCCAGGCAUUGCUCAGC	0.6574	0.0165	0.2943	0.0542	IR sensitizing	644.
hsa-miR-595	MI0003607	GAAAGUGGCCGUGGUGUGUCU	0.8089	0.0082	0.4947	0.0571	IR sensitizing	645.
hsa-miR-596	MI0003608	AAGCCUGCCCGCUCUCCGGG	0.6315	0.0156	0.2701	0.0936	IR sensitizing	646.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-597	MI0003609	UGUGUCACUCGAUGACCACUGU	0.6543	0.0206	1.2019	0.1515	-	647.
hsa-miR-598	MI0003610	UACGUCAUCGUUGUCAUCGUCA	0.8818	0.0156	2.0214	0.4670	IR protective	648.
hsa-miR-599	MI0003611	GUUGUGUCAGUUUAUCAAAC	0.8236	0.0071	0.8765	0.0618	-	649.
hsa-miR-600	MI0003613	ACUUAACAGACAAGAGCCUUGCUC	0.7186	0.0455	0.2020	0.0357	IR sensitizing	650.
hsa-miR-601	MI0003614	UGGUCUAGGAUUUGGAGGAG	0.6073	0.0075	0.2373	0.0500	IR sensitizing	651.
hsa-miR-602	MI0003615	GACACGGGGACAGCUGGGGCCC	0.7976	0.0082	1.2706	0.0643	-	652.
hsa-miR-603	MI0003616	CACACACUGCAAUUACUUUUGC	0.6861	0.0068	0.3129	0.0287	IR sensitizing	653.
hsa-miR-604	MI0003617	AGGUCGCGGAUUCAGGAC	0.1753	0.0127	0.1343	0.0359	Toxic	654.
hsa-miR-605	MI0003618	UAAAUCCCAUGGUGCCUUCUCCU	0.7534	0.0176	0.3836	0.0676	IR sensitizing	655.
hsa-miR-606	MI0003619	AAACUACUGAAAAUCAAAGAU	0.7274	0.0068	1.0708	0.2286	-	656.
hsa-miR-607	MI0003620	GUUCAAUCCAGAUUAUAAC	0.7585	0.0071	0.5614	0.0617	-	657.
hsa-miR-608	MI0003621	AGGGGUGGUUGGGACAGCUCCGU	0.2620	0.0099	0.0577	0.0085	Toxic	658.
hsa-miR-609	MI0003622	AGGGUUUUCUUAUCUCU	0.5675	0.0068	0.1130	0.0267	IR sensitizing	659.
hsa-miR-610	MI0003623	UGAGCUAAUUGUGUGCGGGA	0.9146	0.0125	1.3326	0.0994	-	660.
hsa-miR-611	MI0003624	GCGAGGACCCUCGGGUCUGAC	0.8113	0.0244	3.1278	0.4857	IR protective	661.
hsa-miR-612	MI0003625	GCUGGGCAGGCUUCUGAGCUCCUU	0.7708	0.0091	0.2953	0.0192	IR sensitizing	662.
hsa-miR-613	MI0003626	AGGAAUGUCCUUCUUUUGCC	0.4087	0.0740	0.1433	0.0242	Toxic	663.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-614	MI0003627	GAACGCCUUGUUCUUGCCAGGUGG	0.6889	0.0176	0.8320	0.0181	-	664.
hsa-miR-615	MI0003628	UCCGAGCCUGGGUCUCCUCUU	0.7846	0.0025	1.2496	0.1866	-	665.
hsa-miR-615-5p	MI0003628	GGGGUCCCCGGUGCUCGGAUC	0.7826	0.0126	3.2537	0.5938	IR protective	666.
hsa-miR-616	MI0003629	AGUCAUUGGAGGGUUUGAGCAG	0.7105	0.0154	0.8165	0.0632	-	667.
hsa-miR-616*	MI0003629	ACUCAAACCCUUCAGUGACUU	0.7941	0.0126	1.9116	0.1611	-	668.
hsa-miR-617	MI0003631	AGACUCCCAUUUGAAGGUGGC	0.6074	0.0163	0.1731	0.0135	IR sensitizing	669.
hsa-miR-618	MI0003632	AAACUCUACUUGUCCUUCUGAGU	0.6362	0.0250	0.4019	0.1124	IR sensitizing	670.
hsa-miR-619	MI0003633	GACUGGACAUGUUUGUCCGAGU	0.6414	0.0214	0.3375	0.0715	IR sensitizing	671.
hsa-miR-620	MI0003634	AUGGAGAUAGAUUAGAAAU	0.7084	0.0167	0.5397	0.0243	-	672.
hsa-miR-621	MI0003635	GGCUAGCAACAGCGCUUACCU	0.7510	0.0155	0.2068	0.0320	IR sensitizing	673.
hsa-miR-622	MI0003636	ACAGUCUCUGAGGUUGGAGC	0.9046	0.0134	2.7038	0.6465	IR protective	674.
hsa-miR-623	MI0003637	AUCCCUUGCAGGGCGUUGGGU	0.8219	0.0397	2.2062	0.0574	IR protective	675.
hsa-miR-624	MI0003638	CACAAAGUAUUGGUUUAUACCU	0.6239	0.0114	0.4461	0.0622	IR sensitizing	676.
hsa-miR-624*	MI0003638	UAGUACCAGUACCUUGUGUUA	0.9655	0.0188	0.2953	0.0430	IR sensitizing	677.
hsa-miR-625	MI0003639	AGGGGAAAGUUCUAUAGUCC	0.2739	0.0345	0.1033	0.0304	Toxic	678.
hsa-miR-625*	MI0003639	GACUAUAGAACUUUCCCCCUCA	0.7116	0.0143	0.2208	0.0136	IR sensitizing	679.
hsa-miR-626	MI0003640	AGCUGUCUGAAAAUUGUCUU	0.8906	0.0107	1.8490	0.0199	-	680.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-627	MI0003641	GUGAGUCUCUAGAAAAAGAGGA	0.8221	0.0418	1.6907	0.1858	-	681.
hsa-miR-628	MI0003642	UCUAGUAAGAGUGGCAGUCGA	0.6996	0.0051	0.9057	0.1626	-	682.
hsa-miR-628-5p	MI0003642	AUGCUGACAUUUUACUAGAGG	0.7459	0.0345	0.1549	0.0100	IR sensitizing	683.
hsa-miR-629	MI0003643	UGGGUUUACGUUGGGAGAACU	0.5570	0.0196	0.2582	0.0310	IR sensitizing	684.
hsa-miR-629*	MI0003643	GUUCUCCCAACGUAAGCCCAGC	0.6863	0.0072	0.0951	0.0062	IR sensitizing	685.
hsa-miR-630	MI0003644	AGUAUUCUGUACAGGGAAGGU	0.7773	0.0159	0.2863	0.0662	IR sensitizing	686.
hsa-miR-631	MI0003645	AGACCUGGCCAGACCUCAGC	0.1615	0.0060	0.0613	0.0077	Toxic	687.
hsa-miR-632	MI0003647	GUGUCUGCUUCCUGUGGGA	0.9399	0.0300	1.2700	0.1292	-	688.
hsa-miR-633	MI0003648	CUAAUAGUAUCUACCACAAUAAA	0.8992	0.0149	0.7176	0.0351	-	689.
hsa-miR-634	MI0003649	AACCAGCACCCCAACUUUGGAC	0.6078	0.0142	0.1465	0.0325	IR sensitizing	690.
hsa-miR-635	MI0003650	ACUUGGGCACUGAAACAAGUCC	0.8528	0.0108	0.2309	0.0293	IR sensitizing	691.
hsa-miR-636	MI0003651	UGUGCUUUCUUCUCCGCCCGCA	0.7225	0.0062	1.7883	0.3065	-	692.
hsa-miR-637	MI0003652	ACUGGGGCUUUCGGGCUUCUGCGU	0.2753	0.0997	0.0879	0.0162	Toxic	693.
hsa-miR-638	MI0003653	AGGGAUCGCGGGGCGGUGGGGCCU	0.8444	0.0269	2.1147	0.0481	IR protective	694.
hsa-miR-639	MI0003654	AUCGCUCCGUUGCGAGCGCUGU	0.6498	0.0083	1.5079	0.0576	-	695.
hsa-miR-640	MI0003655	AUGAUCCAGGAACCUGCCUCU	0.6463	0.0554	0.3225	0.0444	IR sensitizing	696.
hsa-miR-641	MI0003656	AAAGACAUAGGAUAGAGUACCCUC	0.9653	0.0093	2.2577	0.0540	IR protective	697.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-642	MI0003657	GUCCUUCUCCAAAGUGUCUUG	0.9330	0.0099	2.2167	0.0338	IR protective	698.
hsa-miR-643	MI0003658	ACUUGUAUGCUAGCUCAGGUAG	0.8890	0.0140	1.9603	0.0840	-	699.
hsa-miR-644	MI0003659	AGUGUGGCUUUUCUUAAGAGC	0.0608	0.0090	0.0480	0.0083	Toxic	700.
hsa-miR-645	MI0003660	UCUAGGCUUGUACUUGCUGA	0.6605	0.0112	0.5028	0.0292	-	701.
hsa-miR-646	MI0003661	AAGCAGCUGCCUCUGAGGC	0.1223	0.0295	0.0642	0.0030	Toxic	702.
hsa-miR-647	MI0003662	GUGGCUGCACUCACUUCUUC	0.0688	0.0023	0.0996	0.0107	Toxic	703.
hsa-miR-648	MI0003663	AAGUGUGCAGGCGACUGGU	0.7487	0.0033	0.1664	0.0020	IR sensitizing	704.
hsa-miR-649	MI0003664	AAACCUUGUUGUUAAGAGUC	0.7175	0.0030	1.1632	0.0345	-	705.
hsa-miR-650	MI0003665	AGGAGGCAGCGCUCACAGGAC	0.2105	0.0215	0.1011	0.0059	Toxic	706.
hsa-miR-651	MI0003666	UUUAGGAUAAGCUUGACUUUUG	0.7502	0.0072	0.9620	0.0514	-	707.
hsa-miR-652	MI0003667	AAUGGCGCCACUAGGGUUGUG	0.7709	0.0078	0.6366	0.1118	-	708.
hsa-miR-653	MI0003674	GUGUUGAAACAAUCUCUACUG	0.7949	0.0019	1.4973	0.2517	-	709.
hsa-miR-654	MI0003676	UGGUGGGCCGCGAACAUGUGC	0.1101	0.0041	0.0489	0.0030	Toxic	710.
hsa-miR-654-3p	MI0003676	UAUGUCUCUGACCAUCACCUU	0.8659	0.0122	1.2998	0.1577	-	711.
hsa-miR-655	MI0003677	AUAUAUAUGGUUAACCUUUU	0.2905	0.0420	0.0589	0.0022	Toxic	712.
hsa-miR-656	MI0003678	AAUAUUAUACAGUAACCUUCU	0.6830	0.0023	0.2882	0.0292	IR sensitizing	713.
hsa-miR-657	MI0003681	GGCAGGUUCUACCCUUCUAGG	0.4618	0.0162	0.1648	0.0010	Toxic	714.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-658	MI0003682	GGCGGAGGGAAGUAGGUCCGUUGGU	0.8937	0.0230	1.8790	0.1013	-	715.
hsa-miR-659	MI0003683	CUUGGUUCAGGAGGGUCCCA	0.6451	0.0122	0.6915	0.0781	-	716.
hsa-miR-660	MI0003684	UACCAUUGCAUUCGGAGUUG	0.8994	0.0159	0.2500	0.0016	IR sensitizing	717.
hsa-miR-661	MI0003669	UGCCUGGUUCUGGCCUGCGCGU	0.5180	0.0122	0.1486	0.0055	IR sensitizing	718.
hsa-miR-662	MI0003670	UCCACGUUGUGGCCACGAG	0.8326	0.0290	1.6693	0.0469	-	719.
hsa-miR-663	MI0003672	AGCGGGGCGCGGGGACCGC	0.6184	0.0008	0.2509	0.0108	IR sensitizing	720.
hsa-miR-665	MI0005563	ACCAGAGGCUAGAGGCCCU	0.2821	0.0050	0.1051	0.0027	Toxic	721.
hsa-miR-668	MI0003761	UGUCACUGGCUCCGCCACUAC	0.8461	0.0164	0.7148	0.0135	-	722.
hsa-miR-671	MI0003760	AGGAAGCCUGGAGGGGCUUGAG	0.7896	0.0102	0.4862	0.0196	IR sensitizing	723.
hsa-miR-671-3p	MI0003760	UCCGGUUCUACGGCUCCACC	0.1364	0.0115	0.0474	0.0021	Toxic	724.
hsa-miR-675	MI0005416	UGGUGCGGAGAGGGCCACAGUG	0.6181	0.0192	0.5753	0.1506	-	725.
hsa-miR-7	MI0000264	UGGAAGACUAGUGAUUUUGUUGU	0.1714	0.0120	0.0911	0.0155	Toxic	726.
hsa-miR-7	MI0000265	UGGAAGACUAGUGAUUUUGUUGU	0.2570	0.0275	0.0978	0.0075	Toxic	727.
hsa-miR-7	MI0000263	UGGAAGACUAGUGAUUUUGUUGU	0.2629	0.0385	0.1305	0.0262	Toxic	728.
hsa-miR-708	MI0005543	AAGGAGCUUACAAUCUAGCUGGG	0.3871	0.0055	0.0467	0.0063	Toxic	729.
hsa-miR-708*	MI0005543	CAACUAGACUGAGCUUCUAG	0.9674	0.0174	0.1646	0.0068	IR sensitizing	730.
hsa-miR-7-1*	MI0000263	CAACAAUACACAGUCGCCAUA	0.9904	0.0335	1.6279	0.0521	-	731.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-7-2*	MI0000264	CAACAAUCCAGUCUACCUGA	0.8262	0.0202	2.3763	0.4132	IR protective	732.
hsa-miR-744	MI0005559	UGCGGGGUAGGGUAAACAGCA	0.1974	0.0020	0.0251	0.0023	Toxic	733.
hsa-miR-744*	MI0005559	CUGUUGCCACUAACCUCUAACCU	0.5920	0.0078	0.0592	0.0072	IR sensitizing	734.
hsa-miR-758	MI0003757	UUUGUGACCUGGUCCACUAACC	0.7816	0.0149	0.1768	0.0055	IR sensitizing	735.
hsa-miR-760	MI0005567	CGGCUCUGGGUCUGUGGGGA	0.8509	0.0185	0.6354	0.0999	-	736.
hsa-miR-765	MI0005116	UGGAGGAGAAGGAAGGUGAUG	0.0857	0.0068	0.0722	0.0142	Toxic	737.
hsa-miR-766	MI0003836	ACUCCAGCCCCACAGCCUCAGC	0.5861	0.0154	0.1659	0.0319	IR sensitizing	738.
hsa-miR-767-3p	MI0003763	UCUGCUCAUACCCCAUGGUUUCU	0.8636	0.0212	0.1810	0.0051	IR sensitizing	739.
hsa-miR-767-5p	MI0003763	UGCACCAUGGUUGUCUGAGCAUG	0.8936	0.0262	0.2445	0.0181	IR sensitizing	740.
hsa-miR-768-3p	MI0005117	UCACAAUGCUGACACUCAAAACUGCUGAC	0.8040	0.0089	0.1908	0.0216	IR sensitizing	741.
hsa-miR-768-5p	MI0005117	GUUGGAGGAUGAAAGUACGGAGUGAU	0.2207	0.0405	0.0926	0.0081	Toxic	742.
hsa-miR-769-3p	MI0003834	CUGGGAUCUCCGGGUCUUGGUU	0.8738	0.0325	0.3271	0.0594	IR sensitizing	743.
hsa-miR-769-5p	MI0003834	UGAGACCUUGGGUUCUGAGCU	0.6996	0.0082	0.2732	0.0441	IR sensitizing	744.
hsa-miR-770-5p	MI0005118	UCCAGUACCACGUGUCAGGGCCA	0.7515	0.0363	0.1724	0.0130	IR sensitizing	745.
hsa-miR-801	MI0005202	GAUUGCUCUGGUGCGGAAUCGAC	0.7025	0.0048	0.1065	0.0138	IR sensitizing	746.
hsa-miR-802	MI0003906	CAGUACAAAAGAUUAUCCUUGU	0.7886	0.0276	0.3697	0.0506	IR sensitizing	747.
hsa-miR-873	MI0005564	GCAGGAACUUGUGAGUCUCCU	0.6987	0.0062	0.2942	0.0211	IR sensitizing	748.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-874	MI0005532	CUGCCCUUGGCCCGGAGGACCGA	1.0246	0.0387	2.6905	0.0877	IR protective	749.
hsa-miR-875-3p	MI0005541	CCUGGAAACACUGAGGUUGUG	0.8499	0.0092	1.5871	0.0540	-	750.
hsa-miR-875-5p	MI0005541	UAUACCUCAGUUUAUCAGGUG	0.7868	0.0206	0.6278	0.0628	-	751.
hsa-miR-876-3p	MI0005542	UGGUGUUUACAAAGUAAUUA	0.2734	0.0087	0.0578	0.0043	Toxic	752.
hsa-miR-876-5p	MI0005542	UGGAUUUCUUUGUAAUACCA	0.7955	0.0084	0.6314	0.0123	-	753.
hsa-miR-877	MI0005561	GUAGAGGAGUUGGCGCAGGG	0.9912	0.0158	1.9139	0.0225	-	754.
hsa-miR-877*	MI0005561	UCCUCUUCUCCCUCCUCCAG	0.8140	0.0146	0.4357	0.0581	IR sensitizing	755.
hsa-miR-885-3p	MI0005560	AGCAGCGGGUGUAGUGGAUA	0.2602	0.0445	0.0882	0.0098	Toxic	756.
hsa-miR-885-5p	MI0005560	UCCAUUACACUACCCUGCCUCU	0.6969	0.0265	0.1925	0.0095	IR sensitizing	757.
hsa-miR-886-3p	MI0005527	CGCGGGUGCUUACUGACCCUU	0.4644	0.0676	0.0382	0.0058	Toxic	758.
hsa-miR-886-5p	MI0005527	CGGUCGGAGUUAGCUCAGCGG	0.7484	0.0032	2.3542	0.2416	IR protective	759.
hsa-miR-887	MI0005562	GUGAACGGGCGCAUCCCGAGG	0.7336	0.0269	0.3010	0.0417	IR sensitizing	760.
hsa-miR-888	MI0005537	UACUAAAAAGCUGUCAGUCA	1.0749	0.0147	2.6597	0.0495	IR protective	761.
hsa-miR-888*	MI0005537	GACUGACACCUUUUGGGUGAA	0.9271	0.0135	0.1030	0.0091	IR sensitizing	762.
hsa-miR-889	MI0005540	UUAAUAUCGGACACCAUUGU	0.6494	0.0133	0.1319	0.0088	IR sensitizing	763.
hsa-miR-890	MI0005533	UACUUGGAAAGGCAUCAGUUG	0.8707	0.0390	0.0533	0.0057	IR sensitizing	764.
hsa-miR-891a	MI0005524	UGCAACGAACCUAGAGCCACUGA	0.7373	0.0084	0.5143	0.1170	-	765.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-891b	MI0005534	UGCAACUACCUGAGUCAUUGA	0.2264	0.0268	0.0583	0.0051	Toxic	766.
hsa-miR-892a	MI0005528	CACUGUGUCCUUUCUGCGUAG	0.6746	0.0066	0.1790	0.0126	IR sensitizing	767.
hsa-miR-892b	MI0005538	CACUGGCUCCUUUCUGGGUAGA	0.8056	0.0304	0.1421	0.0140	IR sensitizing	768.
hsa-miR-9	MI0000467	UCUUUGGUUAUCUAGCUGUAUGA	0.5891	0.0321	0.0715	0.0059	IR sensitizing	769.
hsa-miR-9	MI0000466	UCUUUGGUUAUCUAGCUGUAUGA	0.6023	0.0130	0.2033	0.0356	IR sensitizing	770.
hsa-miR-9	MI0000468	UCUUUGGUUAUCUAGCUGUAUGA	0.6973	0.0338	0.2387	0.0371	IR sensitizing	771.
hsa-miR-9*	MI0000466	AUAAAGCUAGAUAAACCGAAAGU	0.6705	0.0431	0.0735	0.0094	IR sensitizing	772.
hsa-miR-9*	MI0000467	AUAAAGCUAGAUAAACCGAAAGU	0.4757	0.0058	0.0357	0.0084	Toxic	773.
hsa-miR-9*	MI0000468	AUAAAGCUAGAUAAACCGAAAGU	0.4899	0.0497	0.0455	0.0017	Toxic	774.
hsa-miR-92	MI0000093	UAUUGCACUUGUCCCGGCCUGU	0.7725	0.0135	1.0849	0.1993	-	775.
hsa-miR-92	MI0000094	UAUUGCACUUGUCCCGGCCUGU	0.6688	0.0046	2.0861	0.2660	IR protective	776.
hsa-miR-920	MI0005712	GGGGAGCUGUGGAAGACAGUA	0.8542	0.0030	0.9291	0.0372	-	777.
hsa-miR-921	MI0005713	CUAGUGAGGGACAGAACCGAGAUUC	0.7283	0.0074	0.2628	0.0113	IR sensitizing	778.
hsa-miR-922	MI0005714	GCAGCAGAGAAUAGGACUACGUC	0.6947	0.0064	0.3676	0.0405	IR sensitizing	779.
hsa-miR-923	MI0005715	GUCAGCGGAGGAAAGAAACU	0.8434	0.0046	1.3210	0.0718	-	780.
hsa-miR-924	MI0005716	AGAGUCUUGUGAUGUCUUGC	0.6991	0.0101	0.2422	0.0118	IR sensitizing	781.
hsa-miR-92a-1*	MI0000093	AGGUUGGGAUCGGUUGCAAUGCU	0.2934	0.0522	0.0998	0.0209	Toxic	782.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-92a-2*	MI0000094	GGGUGGGGAUUUGCAUUAAC	0.8557	0.0415	0.2502	0.0235	IR sensitizing	783.
hsa-miR-92b	MI0003560	UAUUGCACUCGUCCCGGCCUCC	0.6330	0.0051	1.6427	0.2615	-	784.
hsa-miR-92b*	MI0003560	AGGGACGGGACGCGGUGCAGUG	0.5920	0.0166	0.5061	0.0583	-	785.
hsa-miR-93	MI0000095	CAAAGUCUUGUUCGUGCAGGUAG	0.8551	0.0077	1.0794	0.0701	-	786.
hsa-miR-93*	MI0000095	ACUGCUGAGCUAGCACUUCCCG	0.5672	0.0067	0.0845	0.0062	IR sensitizing	787.
hsa-miR-933	MI0005755	UGUGCGCAGGGAGACCUUCUCCC	0.7827	0.0042	0.5547	0.0200	-	788.
hsa-miR-934	MI0005756	UGUCUACUACUGGAGACACUGG	0.3986	0.0491	0.1013	0.0094	Toxic	789.
hsa-miR-935	MI0005757	CCAGUUAACCGCUUCCGCUACCGC	0.7700	0.0054	0.8101	0.1698	-	790.
hsa-miR-936	MI0005758	ACAGUAGAGGGAGGAUUCGCAG	0.7824	0.0160	0.4115	0.0577	IR sensitizing	791.
hsa-miR-937	MI0005759	AUCCGCGCUCUGACUCUCUGCC	0.6994	0.0103	0.5768	0.0114	-	792.
hsa-miR-938	MI0005760	UGCCCUUAAAGGUAAACCCAGU	0.7252	0.0085	0.8297	0.0190	-	793.
hsa-miR-939	MI0005761	UGGGGAGCUGAGGCUUGGGGGUG	0.8513	0.0178	0.9736	0.1125	-	794.
hsa-miR-940	MI0005762	AAGGCAGGGCCCCCGCUCCCC	0.1697	0.0039	0.0642	0.0036	Toxic	795.
hsa-miR-941	MI0005766	CACCCGCGCUGUGGCACAUUGUC	0.7536	0.0063	0.8579	0.0633	-	796.
hsa-miR-941	MI0005764	CACCCGCGCUGUGGCACAUUGUC	0.7746	0.0053	0.8826	0.0352	-	797.
hsa-miR-941	MI0005765	CACCCGCGCUGUGGCACAUUGUC	0.7438	0.0036	0.9375	0.0317	-	798.
hsa-miR-941	MI0005763	CACCCGCGCUGUGGCACAUUGUC	0.7499	0.0133	1.0242	0.0256	-	799.

Table 1.

MicroRNA	miRBase accession number	Sequence	Cell growth normalized to control		IR response normalized to control		Category	SEQ ID NO:
			Mean (n=4)	SEM	Mean (n=4)	SEM		
hsa-miR-942	MI0005767	UCUUCUCUGUUUUGGCCAUGUG	0.8396	0.0154	0.3676	0.0681	IR sensitizing	800.
hsa-miR-943	MI0005768	CUGACUGUUUGCCGUCUCCAG	0.5568	0.0045	0.1424	0.0055	IR sensitizing	801.
hsa-miR-944	MI0005769	AAAUUAUUGUACAUCGGAUGAG	0.5740	0.0382	0.0681	0.0028	IR sensitizing	802.
hsa-miR-95	MI0000097	UUCACGGGUAUUUAUUGAGCA	0.9062	0.0245	1.4136	0.1202	-	803.
hsa-miR-96	MI0000098	UUUGGCACUAGCACAUUUUUUGCU	0.7501	0.0178	0.4100	0.0196	IR sensitizing	804.
hsa-miR-96*	MI0000098	AAUCAUGUGCAGUGCCAAUAUG	0.6279	0.0026	0.3646	0.0352	IR sensitizing	805.
hsa-miR-98	MI0000100	UGAGGUAGUAAGUUGUAUUGUU	0.7694	0.0314	0.4744	0.0755	IR sensitizing	806.
hsa-miR-99a	MI0000101	AACCCGUAGAUCCGAUCUUGUG	0.7978	0.0412	0.2253	0.0222	IR sensitizing	807.
hsa-miR-99a*	MI0000101	CAAGCUCGCUUCUAUUGGGUCUG	0.8450	0.0018	0.5779	0.1044	-	808.
hsa-miR-99b	MI0000746	CACCCGUAGAACCGACCUUGCG	0.6616	0.0779	0.1692	0.0056	IR sensitizing	809.
hsa-miR-99b*	MI0000746	CAAGCUCGUGUCUGUGGGUCCG	0.8627	0.0318	0.7699	0.2160	-	810.

[0056] Several miRNAs have also been reported to protect cells from IR. As such, inhibition of these miRNAs is an attractive treatment strategy to help overcome radiation resistance. Similarly, these miRNAs serve as biomarkers to predict tumor susceptibility to IR. miR-21 is an oncogenic miRNA that is up-regulated in multiple cancers (Volinia S, et al. (2006) *Proc Natl Acad Sci USA* 103(7):2257-2261.) Previous studies have reported miR-21 to be radiation protective through the regulation of PI3K/AKT signaling and autophagy (Gwak HS, et al. (2012) *PLoS One* 7(10):e47449.). In another example, the cancer associated miR-106b family (Volinia S, et al. (2006) *Proc Natl Acad Sci USA* 103(7):2257-2261.; Hudson RS, et al. (2013) *Oncogene* 32(35):4139-4147.) provides a radiation protective phenotype through the regulation of cell cycle progression (Li B, et al. (2011) *Prostate* 71(6):567-574.). Both miR-21 and miR-106b were confirmed as radiation protective miRNAs in screens described herein. Several additional radiation modifying candidate miRNAs (Li B, et al. (2011) *Prostate* 71(6):567-574.; Czocho JR, Glazer PM (2014) *Antioxid Redox Signal* 21(2):293-312.; Weidhaas JB, et al. (2007) *Cancer Res* 67(23):11111-11116.; Chen G, et al. (2010) *Oncol Rep* 23(4):997-1003.) were supported in studies described herein, indicating the reliability of the screen and analysis. However, some contradictory results were also observed. For example, IR sensitivity was not potently affected by miR-155 in the screens described herein (Gasparini P, et al. (2014) *Proc Natl Acad Sci USA* 111(12):4536-4541.). These results may reflect differences in radiation sensitivity between cancer cell types or anomalies within the library screen. These differences underscore the need to validate each candidate miRNAs for its role in radiation response and DNA repair.

[0057] The p53 status of cancer cells can influence radiation response due to its role in DDR and repair (Mirzayans R, Andrais B, Scott A, Wang YW, Murray D (2013) *Int J Mol Sci* 14(11):22409-22435.; Simone CB 2nd, et al. (2013) *Transl Oncol* 6(5):573-585.). Over half of human cancers have mutated or deleted p53, and p53 is often lost in more advanced disease (Harris CC (1996) *J Natl Cancer Inst* 88(20):1442-1455.). Here, multiple cell lines of differential p53 gene status were applied. Specifically, LNCaP cells are p53 wild-type, where PC3 and DU145 cells are p53 null and mutant, respectively (Simone CB 2nd, et al. (2013) *Transl Oncol* 6(5):573-585.). While the functional screen was completed with WT p53 LNCaP cells, the candidate miRNAs showed common radiation sensitizing effect in p53 wild

type and ablated cell types. Therefore, many of these miRNAs are strong agents to use in combination with IR regardless of the p53 status.

[0058] Examples herein describe two radiation sensitizing miRNAs, miR-890-5p and miR-744-3p. miRNAs may also be administered with a chemotherapeutic agent to sensitize cancer cells to the chemotherapeutic agent. Mechanistic studies confirmed that these miRNAs delayed γ -H2AX resolution and DNA repair. Further experiments demonstrated the polyvalent nature of these miRNAs with their ability to target multiple genes within DDR pathways. miR-890-5p transfection reduced the protein levels of four DDR genes, MAD2L2, WEE1, XPC, and KU80. Suppression of MAD2L2, a mitotic spindle assembly checkpoint protein, is known to cause hypersensitivity to IR and increased γ -H2AX foci formation (Cheung HW, et al. (2006) *Cancer Res* 66(8):4357-4367.; Zhao J, et al. (2011) *J Clin Neurosci* 18(6):827-833.). WEE1, a mitotic checkpoint protein and tyrosine kinase, is also a validated target for enhancing cellular sensitivity to DNA damaging agents (Wang Y, Decker SJ, Sebolt-Leopold J (2004) *Cancer Biol Ther* 3(3):305-313.; Bridges KA, et al. (2011) *Clin Cancer Res* 17(17):5638-5648.). XPC is mutated in xeroderma pigmentosum and functions in nucleotide excision repair (Chavanne F, et al. (2000) *Cancer Res* 60(7):1974-1982.). XPC knock-down also reduces DSB repair and increases cellular sensitivity to DNA damaging agents (Despras E, et al. (2007) *Cancer Res* 67(6):2526-2534.). KU80, encoded by XRCC5, is also a well characterized DDR and repair protein involved in non-homologous end joining and radiation sensitivity (Taccioli GE, et al. (1994) *Science* 265(5177):1442-1445.; Liang F, Romanienko PJ, Weaver DT, Jeggo PA, Jasin M (1996) *Proc Natl Acad Sci USA* 93(17):8929-8933.).

[0059] Thus, miR-890-5p enhances cellular sensitivity to DNA damaging agents through a variety of pathway targets. While it has been hypothesized that individual miRNAs may target multiple genes within the same pathway to produce a given phenotype (Petrocca F, et al. (2008) *Cancer Cell* 13(3):272-286.), this concept has not been significantly challenged. To investigate the multifunctional nature of miR-890-5p to mediate radiation sensitization, siRNA was used to knock-down a primary miR-890-5p target, MAD2L2, to determine if additional radiation sensitivity could be detected through alternate targets. The results demonstrate that miR-890-5p enhances IR sensitivity even after significant MAD2L2 knockdown, supporting the concept that miRNAs can function by targeting multiple genes in related pathways. The knock-down of MAD2L2 did not appear to influence the efficiency of miR-890-5p to suppress a

secondary target, WEE1, suggesting that these mRNAs do not significantly compete for miR-890-5p binding.

[0060] The primary transcript for miR-890-5p is not well characterized, but it is presumed to include miR-888, miR-892a, and miR-892b due to their proximity. The mature miRNAs from this cluster were radiation sensitizing in screens described herein, indicating that this gene region plays a specialized role in DNA repair. Interestingly, miRNAs from this gene region are uniquely expressed at high levels in human epididymis, suggesting a potential role for these miRNAs in sperm maturation or fertility (Landgraf P, et al. (2007) *Cell* 129(7):1401-1414.; Belleannée C, et al. (2012) *PLoS One* 7(4):e34996.). miR-890-5p expression is low or absent in other human tissues, including the prostate (Landgraf P, et al. (2007) *Cell* 129(7):1401-1414.). Notably, the incidence of epididymal tumors is very rare and represents at most 0.03% of all male cancers, in sharp contrast to almost 20% for prostate cancer in Western countries (Yeung CH, Wang K, Cooper TG (2012) *Asian J Androl* 14(3):465-475.). As described herein, the miR-890-5p gene cluster contributes to this differential cancer susceptibility due to increased cellular sensitivity to DNA damage.

[0061] The results presented herein support the potential use of miR-890-5p and miR-744-3p as a radiation sensitizing agent. miRNA mimetics and inhibitors have shown promise as therapeutic agents in pre-clinical models and a few are being translated for human clinical trials. For example a miR-122 inhibitor, Miravirsen, is currently in clinical trials for the treatment of Hepatitis C (Janssen HL, et al. (2013) *N Engl J Med* 368(18):1685-1694.). Further, a liposome-based miR-34 mimic (MRX34) entered Phase I clinical trials in patients with advanced hepatocellular carcinoma in 2013 (Ling H, Fabbri M, Calin GA (2013) *Nat Rev Drug Discov* 12(11):847-865.). Demonstrated herein, a liposomally-delivered miR-890-5p mimetic enhanced the therapeutic effect of IR in established prostate tumors. IR is a commonly applied treatment for multiple cancer types, including prostate cancer. It can be administered through targeted external beam radiation therapy, localized radioactive seed placement, or systemically targeted radiotherapeutics. Thus the selective delivery miR-890-5p to tumors, or activation of endogenous miR-890-5p in cancer cells, may significantly enhance the therapeutic index of IR or other DNA damaging therapies by preventing DNA repair.

[0062] In summary, a series of high-throughput functional screens have identified several miRNAs capable of regulating cancer cell radiation sensitivity and DNA repair. miR-890-5p

sensitizes cancer cells to IR through multiple gene targets, including MAD2L2 supporting the concept that a single miRNA can simultaneously regulate multiple genes within a single pathway. These results suggest that miRNAs may have therapeutic potential in the treatment of cancers with IR or with an additional chemotherapeutic agent.

[0063] A composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with a chemotherapeutic agent. The chemotherapeutic agent (also referred to as an anti-neoplastic agent or anti-proliferative agent) can be an alkylating agent; an antibiotic; an anti-metabolite; a detoxifying agent; an interferon; a polyclonal or monoclonal antibody; an EGFR inhibitor; a HER2 inhibitor; a histone deacetylase inhibitor; a hormone; a mitotic inhibitor; an MTOR inhibitor; a multi-kinase inhibitor; a serine/threonine kinase inhibitor; a tyrosine kinase inhibitors; a VEGF/VEGFR inhibitor; a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, an inhibitor of a molecular target or enzyme (*e.g.*, a kinase inhibitor), a cytidine analogue drug or any chemotherapeutic, anti-neoplastic or anti-proliferative agent listed in www.cancer.org/docroot/cdg/cdg_0.asp.

[0064] Exemplary alkylating agents include, but are not limited to, cyclophosphamide (Cytoxan; Neosar); chlorambucil (Leukeran); melphalan (Alkeran); carmustine (BiCNU); busulfan (Busulfex); lomustine (CeeNU); dacarbazine (DTIC-Dome); oxaliplatin (Eloxatin); carmustine (Gliadel); ifosfamide (Ifex); mechlorethamine (Mustargen); busulfan (Myleran); carboplatin (Paraplatin); cisplatin (CDDP; Platinol); temozolomide (Temodar); thiotepe (Thioplex); bendamustine (Treanda); or streptozocin (Zanosar).

[0065] Exemplary antibiotics include, but are not limited to, doxorubicin (Adriamycin); doxorubicin liposomal (Doxil); mitoxantrone (Novantrone); bleomycin (Blenoxane); daunorubicin (Cerubidine); daunorubicin liposomal (DaunoXome); dactinomycin (Cosmegen); epirubicin (Ellence); idarubicin (Idamycin); plicamycin (Mithracin); mitomycin (Mutamycin); pentostatin (Nipent); or valrubicin (Valstar).

[0066] Exemplary anti-metabolites include, but are not limited to, fluorouracil (Adrucil); capecitabine (Xeloda); hydroxyurea (Hydrea); mercaptopurine (Purinethol); pemetrexed (Alimta); fludarabine (Fludara); nelarabine (Arranon); cladribine (Cladribine Novaplus); clofarabine (Clolar); cytarabine (Cytosar-U); decitabine (Dacogen); cytarabine liposomal

(DepoCyt); hydroxyurea (Droxia); pralatrexate (Folotyn); floxuridine (FUDR); gemcitabine (Gemzar); cladribine (Leustatin); fludarabine (Oforta); methotrexate (MTX; Rheumatrex); methotrexate (Trexall); thioguanine (Tabloid); TS-1 or cytarabine (Tarabine PFS).

[0067] Exemplary detoxifying agents include, but are not limited to, amifostine (Ethyol) or mesna (Mesnex).

[0068] Exemplary interferons include, but are not limited to, interferon alfa-2b (Intron A) or interferon alfa-2a (Roferon-A).

[0069] Exemplary polyclonal or monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin); ofatumumab (Arzerra); bevacizumab (Avastin); rituximab (Rituxan); cetuximab (Erbix); panitumumab (Vectibix); tositumomab/iodine¹³¹ tositumomab (Bexxar); alemtuzumab (Campath); ibritumomab (Zevalin; In-111; Y-90 Zevalin); gemtuzumab (Mylotarg); eculizumab (Soliris) ordenosumab.

[0070] Exemplary EGFR inhibitors include, but are not limited to, gefitinib (Iressa); lapatinib (Tykerb); cetuximab (Erbix); erlotinib (Tarceva); panitumumab (Vectibix); PKI-166; canertinib (CI-1033); matuzumab (Emd7200) or EKB-569.

[0071] Exemplary HER2 inhibitors include, but are not limited to, trastuzumab (Herceptin); lapatinib (Tykerb) or AC-480.

[0072] Histone Deacetylase Inhibitors include, but are not limited to, vorinostat (Zolinza).

[0073] Exemplary hormones include, but are not limited to, tamoxifen (Soltamox; Nolvadex); raloxifene (Evista); megestrol (Megace); leuprolide (Lupron; Lupron Depot; Eligard; Viadur) ; fulvestrant (Faslodex); letrozole (Femara); triptorelin (Trelstar LA; Trelstar Depot) ; exemestane (Aromasin) ; goserelin (Zoladex) ; bicalutamide (Casodex); anastrozole (Arimidex); fluoxymesterone (Androxy; Halotestin); medroxyprogesterone (Provera; Depo-Provera); estramustine (Emcyt); flutamide (Eulexin); toremifene (Fareston); degarelix (Firmagon); nilutamide (Nilandron); abarelix (Plenaxis); or testolactone (Teslac).

[0074] Exemplary mitotic inhibitors include, but are not limited to, paclitaxel (Taxol; Onxol; Abraxane); docetaxel (Taxotere); vincristine (Oncovin; Vincasar PFS); vinblastine (Velban); etoposide (Toposar; Etopophos; VePesid); teniposide (Vumon); ixabepilone (Ixempra); nocodazole; epothilone; vinorelbine (Navelbine); camptothecin (CPT); irinotecan (Camptosar); topotecan (Hycamtin); amsacrine or lamellarin D (LAM-D).

[0075] Exemplary MTOR inhibitors include, but are not limited to, everolimus (Afinitor) or temsirolimus (Torisel); rapamune, ridaforolimus; or AP23573.

[0076] Exemplary multi-kinase inhibitors include, but are not limited to, sorafenib (Nexavar); sunitinib (Sutent); BIBW 2992; E7080; Zd6474; PKC-412; motesanib; or AP24534.

[0077] Exemplary serine/threonine kinase inhibitors include, but are not limited to, ruboxistaurin; eril/easudil hydrochloride; flavopiridol; seliciclib (CYC202; Roscovitrine); SNS-032 (BMS-387032); Pkc412; bryostatin; KAI-9803; SF1126; VX-680; Azd1152; Arry-142886 (AZD-6244); SCIO-469; GW681323; CC-401; CEP-1347 or PD 332991.

[0078] Exemplary tyrosine kinase inhibitors include, but are not limited to, erlotinib (Tarceva); gefitinib (Iressa); imatinib (Gleevec); sorafenib (Nexavar); sunitinib (Sutent); trastuzumab (Herceptin); bevacizumab (Avastin); rituximab (Rituxan); lapatinib (Tykerb); cetuximab (Erbix); panitumumab (Vectibix); everolimus (Afinitor); alemtuzumab (Campath); gemtuzumab (Mylotarg); temsirolimus (Torisel); pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna); vatalanib (Ptk787; ZK222584); CEP-701; SU5614; MLN518; XL999; VX-322; Azd0530; BMS-354825; SKI-606 CP-690; AG-490; WHI-P154; WHI-P131; AC-220; or AMG888.

[0079] Exemplary VEGF/VEGFR inhibitors include, but are not limited to, bevacizumab (Avastin); sorafenib (Nexavar); sunitinib (Sutent); ranibizumab; pegaptanib; or vandetinib.

[0080] Exemplary microtubule targeting drugs include, but are not limited to, paclitaxel, docetaxel, vincristin, vinblastin, nocodazole, epothilones and navelbine.

[0081] Exemplary topoisomerase poison drugs include, but are not limited to, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin and idarubicin.

[0082] Exemplary taxanes or taxane derivatives include, but are not limited to, paclitaxel and docetaxol.

[0083] Exemplary general chemotherapeutic, anti-neoplastic, anti-proliferative agents include, but are not limited to, altretamine (Hexalen); isotretinoin (Accutane; Amnesteem; Claravis; Sotret); tretinoin (Vesanoid); azacitidine (Vidaza); bortezomib (Velcade) asparaginase (Elspar); levamisole (Ergamisol); mitotane (Lysodren); procarbazine (Matulane); pegaspargase (Oncaspar); denileukin diftitox (Ontak); porfimer (Photofrin); aldesleukin (Proleukin); lenalidomide (Revlimid); bexarotene (Targretin); thalidomide (Thalomid); temsirolimus

(Torisel); arsenic trioxide (Trisenox); verteporfin (Visudyne); mimosine (Leucenol); (1M tegafur - 0.4 M 5-chloro-2,4-dihydroxypyrimidine - 1 M potassium oxonate) or lovastatin.

[0084] In another aspect, the second chemotherapeutic agent can be a cytokine such as G-CSF (granulocyte colony stimulating factor). In another aspect, a composition the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, analog or derivative thereof, may be administered in combination with radiation therapy. Radiation therapy can also be administered in combination with a composition of the present invention and another chemotherapeutic agent described herein as part of a multiple agent therapy. In yet another aspect, a composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, mimetic, analog or derivative thereof, may be administered in combination with standard chemotherapy combinations such as, but not restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, adriamycin and 5-fluorouracil), AC (adriamycin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (adriamycin, cyclophosphamide, and paclitaxel), rituximab, Xeloda (capecitabine), Cisplatin (CDDP), Carboplatin, TS-1 (tegafur, gimestat and otaostat potassium at a molar ratio of 1:0.4:1), Camptothecin-11 (CPT-11, Irinotecan or Camptosar™) or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

[0085] In preferred embodiments, a composition of the present invention, or a pharmaceutically acceptable salt, prodrug, metabolite, polymorph or solvate thereof, may be administered with an inhibitor of an enzyme, such as a receptor or non-receptor kinase. Receptor and non-receptor kinases of the invention are, for example, tyrosine kinases or serine/threonine kinases. Kinase inhibitors of the invention are small molecules, polynucleic acids, polypeptides, or antibodies.

[0086] Exemplary kinase inhibitors include, but are not limited to, Bevacizumab (targets VEGF), BIBW 2992 (targets EGFR and Erb2), Cetuximab/Erbitux (targets Erb1), Imatinib/Gleevec (targets Bcr-Abl), Trastuzumab (targets Erb2), Gefitinib/Iressa (targets EGFR), Ranibizumab (targets VEGF), Pegaptanib (targets VEGF), Erlotinib/Tarceva (targets Erb1), Nilotinib (targets Bcr-Abl), Lapatinib (targets Erb1 and Erb2/Her2), GW-572016/lapatinib ditosylate (targets HER2/Erb2), Panitumumab/Vectibix (targets EGFR), Vandetinib (targets RET/VEGFR), E7080 (multiple targets including RET and VEGFR), Herceptin (targets HER2/Erb2), PKI-166 (targets EGFR), Canertinib/CI-1033 (targets EGFR), Sunitinib/SU-11464/Sutent (targets EGFR and FLT3), Matuzumab/Emd7200 (targets EGFR), EKB-569 (targets EGFR), Zd6474 (targets EGFR

and VEGFR), PKC-412 (targets VEGFR and FLT3), Vatalanib/Ptk787/ZK222584 (targets VEGFR), CEP-701 (targets FLT3), SU5614 (targets FLT3), MLN518 (targets FLT3), XL999 (targets FLT3), VX-322 (targets FLT3), Azd0530 (targets SRC), BMS-354825 (targets SRC), SKI-606 (targets SRC), CP-690 (targets JAK), AG-490 (targets JAK), WHI-P154 (targets JAK), WHI-P131 (targets JAK), sorafenib/Nexavar (targets RAF kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , KIT, FLT-3, and RET), Dasatinib/Sprycel (BCR/ABL and Src), AC-220 (targets Flt3), AC-480 (targets all HER proteins, “panHER”), Motesanib diphosphate (targets VEGF1-3, PDGFR, and c-kit), Denosumab (targets RANKL, inhibits SRC), AMG888 (targets HER3), and AP24534 (multiple targets including Flt3).

[0087] Exemplary serine/threonine kinase inhibitors include, but are not limited to, Rapamune (targets mTOR/FRAP1), Deforolimus (targets mTOR), Certican/Everolimus (targets mTOR/FRAP1), AP23573 (targets mTOR/FRAP1), Erii/Fasudil hydrochloride (targets RHO), Flavopiridol (targets CDK), Seliciclib/CYC202/Roscovitine (targets CDK), SNS-032/BMS-387032 (targets CDK), Ruboxistaurin (targets PKC), Pkc412 (targets PKC), Bryostatin (targets PKC), KAI-9803 (targets PKC), SF1126 (targets PI3K), VX-680 (targets Aurora kinase), Azd1152 (targets Aurora kinase), Arry-142886/AZD-6244 (targets MAP/MEK), SCIO-469 (targets MAP/MEK), GW681323 (targets MAP/MEK), CC-401 (targets JNK), CEP-1347 (targets JNK), and PD 332991 (targets CDK).

[0088] The present invention also provides pharmaceutical compositions comprising a composition of each of the miRNA described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0089] A “pharmaceutical composition” is a formulation containing the compositions of the present invention in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed composition or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal,

parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a composition of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active composition is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[0090] As used herein, the phrase “pharmaceutically acceptable” refers to those compositions, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0091] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0092] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0093] A composition or pharmaceutical composition of the invention can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a composition of the invention may be injected directly into

tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not as high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0094] The term “therapeutically effective amount”, as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In a preferred aspect, the disease or condition to be treated is cancer. In another aspect, the disease or condition to be treated is a cell proliferative disorder.

[0095] For any composition, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0096] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered

every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0097] The pharmaceutical compositions containing active compositions of the present invention may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compositions into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0098] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability 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 (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can 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. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0099] Sterile injectable solutions can be prepared by incorporating the active composition in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are

prepared by incorporating the active composition into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0100] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active composition can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the composition in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compositions of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0101] For administration by inhalation, the compositions are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0102] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compositions are formulated into ointments, salves, gels, or creams as generally known in the art.

[0103] The active compositions can be prepared with pharmaceutically acceptable carriers that will protect the composition against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable,

biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0104] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active composition calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active composition and the particular therapeutic effect to be achieved.

[0105] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the invention vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term “dosage effective manner” refers to amount of an active composition to produce the desired biological effect in a subject or cell.

[0106] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

EXAMPLES

[0107] Example 1. Materials and Methods

[0108] The human prostate cancer cell lines LNCaP, C4-2, PC3 and DU145 were purchased from the American Type Culture Collection (Manassas, VA). The cells were maintained in RPMI 1640 medium (Cellgro, Manassas, VA) containing 10% fetal bovine serum (FBS), 5 µg/ml ciprofloxacin (USBio, Swampscott, MA) and 5 µg/ml Gentamicin (Quality Biological, Gaithersburg, MD). LNCaP-MLuc and PC3-MLuc cells were previously developed (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.) and maintained in RPMI 1640 containing 10% FBS, 5 µg/ml ciprofloxacin and 5 µg/ml Gentamicin and 5 µg/mL Blastocidin (Invitrogen, Grand Island, NY). The cells were incubated at 37°C in a humidified atmosphere of 95% air and 5% CO₂. Athymic nude mice (nu/nu) aged 6 weeks were purchased from Harlan Laboratories Inc. (Indianapolis, IN) and maintained in a temperature-controlled, pathogen-free room. All animals were handled according to the approved protocols and guidelines of Animal Care and Use Committee at Johns Hopkins University.

[0109] MLuc viability assay

[0110] MLuc cell viability assays were completed as previously described (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.). Two days before IR, LNCaP-MLuc and PC3-MLuc cells stably transfected with the pDonor-hβ-Actin-hMLuc vector were transfected with miRNA mimetics and/or siRNAs. On day 0, the cells were irradiated (4Gy) or untreated. On day 11, the cell culture media was then assayed for MLuc activity. The prostate cancer MLuc cell viability assays were completed as previously described (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.). Two days before IR, LNCaP-MLuc and PC3-MLuc stably transfected with the pDonor-hβ-Actin-hMLuc vector were plated at low density and transfected with miRNA mimetics and/or siRNAs using Lipofectamine 2000 or Lipofectamine RNAiMax (Invitrogen). On day 0, the cells were irradiated (4 Gy in a Gammacell 40 [Nordion] 137Cs radiator at approximately 0.5 Gy/min) or untreated. On day 11, 50 µl cell culture media was then assayed for MLuc activity to quantify the relative cell density using a Renilla buffer, consisting of PBS with 1.43 µM coelenterazine. The MLuc activities were read in a Perkin Elmer Micro Beta luminometer.

[0111] High-throughput functional screening using miRNA library

[0112] Two days before IR, LNCaP-MLuc cells were transfected with 20 nM of 810 different miRNA mimics. Each miRNA was transfected in quadruplicate. Control miRNA and DNAPK siRNA were included in each 96 well plate (sequences in Table 2).

Table 2. The sequence of siRNAs used in this study.

siRNA		
Name	sense	anti-sense
DNAPK	UUCGGCUAACUCGCCAGUUUA (SEQ ID NO: 811)	UAAACUGGCGAGUUAGCCGAA (SEQ ID NO: 812)
MAD2L2	CACCCGGAGCUGAAUCAGUAU (SEQ ID NO: 813)	AUACUGAUUCAGCUCCGGGUG (SEQ ID NO: 814)

Half of the plates were irradiated (4Gy) 48 h after transfection, while the other half remained untreated. Eleven days after IR, MLuc activity was quantified and normalized to the control miRNA. Two days before IR, 2×10^3 LNCaP-MLuc cells were transfected with 20 nM of 810 different miRNA mimics using Lipofectamine 2000 (Invitrogen) in individual wells of 96 well plates. Each miRNA was transfected in quadruplicate with control miRNA and DNAPK siRNA in each 96 well plate. Half of the plates were irradiated 48 h after transfection (4 Gy), while the other half remained untreated. Seven days after irradiation, 50 μ l of media was removed and replaced with 50 μ l of fresh media. Eleven days after irradiation, MLuc activity was examined to quantify viable cell density, normalizing to the control miRNA. Toxic miRNAs, which inhibited cell growth by over 50% in the absence of IR on day 11, were excluded from the classification for radiation sensitization. Radiosensitizing or radioprotective miRNAs were defined as those which increased cell death by over 50% or increased cell survival by over 2 fold, respectively.

[0113] Clonogenic assay

[0114] DU145 cells were transfected with 20 nM control or candidate miRNAs and grown for 48 h, after which cell dilutions were plated and irradiated immediately at different doses. The cells were grown for 14 days. Colonies with greater than 30 cells were scored and surviving fraction was calculated as previously described (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.). Clonogenic survival assays were performed with 8

$\times 10^5$ DU145 cells transfected with 20 nM control or candidate miRNAs and grown for 48 h, after which cell dilutions were plated into 25 cm³ culture flasks and irradiated immediately. Radiation exposures were carried out as described above at 0, 2.5, 5, 7.5 and 10 Gy. The cells were grown for 14 days, fixed and stained with crystal violet; colonies with greater than 30 cells were scored, and surviving fraction was calculated as previously described (Ni X, et al. (2011) *J Clin Invest* 121(6):2383-2390). Survival curves were fitted by GraphPad Prism software (GraphPad Software, La Jolla, CA) by nonlinear regression analysis and a user defined equation for cell survival analysis due to radiation injury.

[0115] γ -H2AX foci formation

[0116] DU145 cells were transfected with 20 nM of control or candidate miRNAs and were seeded on glass slides. The cells were incubated for 48 h and then irradiated (4 Gy) or untreated. The γ -H2AX foci formation was evaluated at 1, 4, 8, 12 and 24 h after IR by immunofluorescent microscopy. The percentage of cells containing >10 fluorescent foci was calculated as previously reported (Cheung HW, et al. (2006) *Cancer Res* 66(8):4357-4367.). DU145 cells were transfected with 20 nM of control or candidate miRNAs and were seeded at 8×10^4 cells/well on 4 chamber polystyrene vessel tissue culture treated glass slides. The cells were incubated for 48 h and then irradiated (4 Gy) or untreated. The γ -H2AX foci formation was evaluated at 1, 4, 8, 12 and 24 h after IR. The cells were washed with PBS, and fixed with 4% formaldehyde for 15 min, followed by treatment with 0.2% Triton X-100 for 10 min. The cells were blocked with 1% BSA in PBS for 1 h and were incubated with γ -H2AX antibody (1:1000) for 30 min. The cells were washed and labeled with a 1:1000 dilution of Alexa Fluor antibody (Invitrogen) for 30 min. Cellular DNA was counterstained with Prolong Gold with DAPI (Invitrogen). Fluorescent signals were visualized with a Nikon eclipse TE 2000E microscope and analyzed by NIS-Elements advanced Research version 3.2 software (Nikon, Tokyo, Japan). Images were photographed at the same exposure time under a $\times 20$ objective. Over 300 cells were counted from more than three random fields under a $\times 20$ objective for each experiment, and the percentage of cells containing >10 fluorescent foci was calculated as previously reported (Cheung HW, et al. (2006) *Cancer Res* 66(8):4357-4367.).

[0117] Comet assay

[0118] The comet assay was carried out under neutral pH conditions using CometAssay® from Trevigen (Gaithersburg, MD). Comets were imaged by fluorescent microscopy and analyzed

using CometScore. The comet assay was carried out under neutral pH conditions using the CometAssay® from Trevigen (Gaithersburg, MD). Briefly, cells were mixed with low melting point agarose and plated on microscope slides and allowed to gel. Cells were then lysed under neutral buffer followed by rinse in TBE buffer (10.8 % [w/v] tris base, 5.5% [w/v] boric acid, 0.93% [w/v] EDTA). After electrophoresis in TBE buffer for 40 min at 1 V/cm, slides were washed in water and dehydrated with ethanol, air dried overnight and then treated with SYBR Green for DNA staining. Comets were imaged Zeiss Imager.Z1 fluorescent microscopy (Carl Zeiss AG, Oberkochen, Germany) and analyzed using the software CometScore (Autocomet.com). The tail moment was calculated as the average of at least 50 comets.

[0119] 3'UTR constructs

[0120] The 3'UTR regions of the targets were amplified from 293T genomic DNA (human embryonic kidney cells) by PCR. Primer sequences were designed to incorporate *SpeI* and *HindIII* restriction enzyme sites (Table 3). PCR products were inserted into the *SpeI* and *HindIII* cloning site of the pMIR-REPORT luciferase expression reporter vector (Ambion, Grand Island, NY) to generate pMIR-3'UTR. The mutant pMIR-3'UTR reporter vector was generated using QuikChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies, Columbia, MD) according to the manufacturer's instructions (Table 3).

Table 3. The sequence of primers used in this study.

Primers		
Primers for 3'UTR cloning		
Name	Forward	Reverse
MAD2L2 3'UTR	GGACTAGTCACCCCACTGATGCCCAA AC (SEQ ID NO: 815)	CCCAAGCTTGGGGCCCCTTTATTGAAAC (SEQ ID NO: 816)
RAD23B 3'UTR	GGACTAGTAAATCAGCTTTTGCAGGT C (SEQ ID NO: 817)	CCCAAGCTTGCCTCCCACCCCAAGTATTTA (SEQ ID NO: 818)
Primers for mutant pMIR-3'UTR reporter vector		
Name	Forward	Reverse
Mut-MAD2L2	CTGCATGGCTGCCCTGATTTAGAGTG CTCTT ATCGCCTC (SEQ ID NO: 819)	GAGGCGATAAGAGCACTCTAAATCAGGGCA GCCATGCAG (SEQ ID NO: 820)
Mut-RAD23B	CTAGAATTTACAGTCTCTGTTTCATGT AGACACTGGATAATGGCTTTGTG (SEQ ID NO: 821)	CACAAAGCCATTATCCAGTGTCTACATGAAA CAGAGACTGTAAATTCTAG (SEQ ID NO: 822)

[0121] 3'UTR Dual Luciferase Assay

[0122] LNCaP cells were transfected with 20 nM control or miRNA mimics, 80 ng pMIR-3'UTR reporter vector and 20 ng of reference pRL-CMV *Renilla* reporter vector. After 48 h incubation, the reporter activity was assessed using a Dual Luciferase Enzyme Assay. Firefly luciferase was normalized against the internal control *Renilla* luciferase. LNCaP cells were transfected by Lipofectamine 2000 with 20 nM control or miRNA mimics, 80 ng pMIR-3'UTR reporter vector and 20 ng of reference pRL-CMV *Renilla* reporter vector. After 48 h incubation, the reporter activity was assessed using a Dual Luciferase Enzyme Assay. The firefly luciferase assay buffer consisted of 25 mM glycylglycine, 15 mM K_2HPO_4 (pH 7.8), 4 mM EGTA, 2 mM ATP, 1 mM DTT, 15 mM $MgSO_4$, 60 μ M CoA, 75 μ M luciferin, with the final pH adjusted to 8.0. The *Renilla* assay buffer was made as follows: 1.1 M NaCl, 2.2 mM Na₂EDTA, 0.22 M K_2HPO_4 (pH 5.1), 0.44 mg/mL BSA, 1.3 mM NaN₃, 1.43 μ M coelenterazine, with the final pH adjusted to 5.0. Light emission was measured in a Wallac 1450 Microbeta Jet Luminescence Reader. Firefly luciferase was first read and signal normalized against the internal control *Renilla* luciferase.

[0123] Western blot analysis

[0124] Cells were transfected with miRNA mimics or siRNAs and incubated for 48 h. MAD2L2, RAD23B, WEE1, XPC, KU80, XLF and MCL1 antibodies were applied to western blotting. ACTB was used as a control for protein loading. Prostate cancer cells were transfected with miRNA mimics or siRNAs and were incubated for 48 h. Cells were harvested and lysed in RIPA lysis buffer. Protein samples were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The separated proteins were transferred onto polyvinylidene fluoride membranes, and the membranes were then blocked with odyssey blocking buffer and incubated overnight at 4°C with anti-MAD2L2 (1:1,000), anti-RAD23B (1:500), anti-WEE1 (1:1000), anti-XPC (1:1000), anti-KU80 (1:1000), anti-XLF (1:1000), anti-MCL1 (1:1000) or anti-ACTB (1:10,000) antibodies. The membranes were washed and labelled with a 1:20,000 dilution of IRDye 680LT anti-mouse or a 1:15,000 dilution of IRDye 800CW anti-rabbit secondary antibody (LI-COR, Lincoln, NE) at room temperature for approximately 1 h. Images were captured and analyzed with an Odyssey infrared imaging system (LI-COR).

[0125] In vivo tumor models

[0126] The animal studies were performed according to the protocols approved by the Animal Care and Use Committee at Johns Hopkins University. Athymic nude mice (nu/nu) aged 6 weeks were inoculated with 5×10^6 DU145 cells subcutaneously. Cohorts of similar tumor volume were randomized and directly injected with PBS, 12.5 μ g of liposomal control miRNA mimetic, or liposomal miR-890-5p mimetic. Two days after injection (day 0) radiation groups received 6 Gy local IR. The tumor volume was calculated according to the formula: tumor volume (cm^3) = $l \times w \times h \times 0.52$. Tumor response was determined as reaching 4 times as its initial size as previously reported (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.). Athymic nude mice (nu/nu) aged 6 weeks were inoculated with 5×10^6 DU145 cells subcutaneously in left thigh. When tumor size reached 0.1 – 0.3 cm^3 in diameter, the treatment was started. Tumors were randomized into 5 groups, including PBS, control miRNA, miR-890, control miRNA plus IR and miR-890-5p plus IR. Liposomal control miRNA mimetic, or liposomal miR-890-5p mimetic were prepared using the MaxSuppressor™ In Vivo RNA-LANCER II kit (Bioo Scientific, Austin, TX) according to the manufacturer's instructions. Mice were anesthetized with isoflurane, and then, tumors were directly injected with total 50 μ l of reagents; PBS, 12.5 μ g of liposomal control miRNA mimetic, or liposomal miR-890-5p mimetic. Two days after injection (day 0), radiation groups received 6 Gy local IR (7.14 Gy/min) using a J.L. Shepherd Mark 137Cs irradiator with the body shielded from the source. Tumors were measured every 2 days and the tumor volume was calculated according to the formula; tumor volume (cm^3) = length $\times$ width $\times$ height $\times$ 0.52. Tumor response was determined as reaching 4 times its volume as its initial size as previously reported (Ni X, et al. (2011) *J Clin Invest* 121(6):2383-2390). Two animals were eliminated from the study due to illness and failure of progressive tumor growth. The animal studies were performed according to the protocols approved by the Animal Care and Use Committee at Johns Hopkins University.

[0127] Statistical analyses

[0128] Assays were analyzed by 2-tailed, unpaired Student's t-test or 2-way ANOVA. Kaplan-Meier analysis was performed by log-rank (Mantel-Cox). $P < 0.05$ was considered statistically significant. The results are reported as the mean $\pm$ standard error (S.E.) or standard deviation (S.D.). The differences between groups were evaluated by 2-tailed, unpaired Student's t-test. The IC_{50} value was calculated using GraphPad Prism 5 software. Tumor volume was evaluated by 2-way ANOVA. For the extension of tumor quadrupling

experiments, events (animals whose tumor volume was not yet 4-fold the size at injection) were plotted on a Kaplan-Meier curve and analyzed by log-rank (Mantel-Cox) test as previously reported (Ni X, et al. (2011) *J Clin Invest* 121(6):2383-2390). $P < 0.05$ was considered statistically significant.

[0129] Example 2. High-throughput screening identifies miRNAs which modulate prostate cancer growth, survival and radiosensitivity.

[0130] A previously developed bioluminescent Metridia Luciferase (MLuc) viability assay (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.), was used to measure cellular sensitivity to IR following the transfection of miRNA mimetics. With this assay the expression of a secreted humanized MLuc reporter is controlled by the human β -actin promoter and enhancer, and bioluminescent activity corresponds linearly with viable cell number (Lupold SE, Johnson T, Chowdhury WH, Rodriguez R (2012) *PLoS One* 7(5):e36535.9). One prostate cancer cell line, LNCaP-MLuc, was applied to screen a library of 810 human miRNA mimetics. A schematic representation of the experimental design is shown in Fig. 1A. Briefly, LNCaP-MLuc cells were separately transfected with individual miRNA mimetics, or control miRNAs, in replicates in multiwell plate format. After 48 h, one group of cells was irradiated (4 Gy), while the other group remained untreated. The secreted MLuc activity was then quantified on the eleventh day to measure relative cell viability and therapeutic effect. A positive control siRNA targeting DNAPK was utilized for radiation sensitization (Figs. 8A and 8B). Analysis of duplicate samples indicates assay reproducibility (Figs. 9A and 9B).

[0131] MLuc activity, representing viable cell density over eleven days, is shown in Fig. 1B for both irradiated cells (red) and non-irradiated cells (blue). The results are organized as a waterfall plot based on radiosensitivity, with the most radiation sensitizing miRNAs on the left, leading to the most radiation protective miRNAs on the right. The results indicate that over half of the miRNAs studied enhanced cellular sensitivity to IR, when compared to a control miRNA, while a much smaller percentage of miRNAs was radiation protective. Many miRNAs belonging to the same families produced matching radiosensitization phenotypes. For example, miRNAs from the miR-15/16 and miR-1/133 families were each observed to be radiation sensitizing, whereas miRNAs from the miR-106b family were found to be radioprotective (Fig. 10). The results for all miRNAs are available in Table 1.

[0132] The experimental design also provided data on cellular responses to miRNA mimetics in the absence of irradiation (Fig. 1C). It is notable that the majority of miRNAs reduced viable cell density, when compared to the control miRNA. These results are consistent with the common global miRNA down-regulation observed in human cancers (Lu J, et al. (2005) *Nature* 435(7043):834-838.). For the purpose of characterizing cellular responses, the miRNAs were grouped into four categories (Fig. 1D, Table 1). miRNAs which reduced growth or viability by over 50% in the absence of IR were termed as toxic miRNAs (purple). Non-toxic miRNAs which enhanced radiation induced cell death by over 50% were considered radiation sensitizing miRNAs (red), and miRNAs which increased cell survival by over 2-fold after irradiation were considered radioprotective (blue). Among 810 miRNAs, 75 (9.3%) were identified as radioprotective, 324 (40.0%) were identified as radiosensitizing, and 127 (15.7%) were considered toxic (Fig. 1D, Table 1).

[0133] Validation of candidate radiation sensitizing miRNAs

[0134] The top 15 candidate radiation sensitizing miRNAs were selected for repeat assays using two reporter cell lines, LNCaP-MLuc and PC3-MLuc (Fig. 2). All 15 candidates were validated as radiation sensitizing in LNCaP-MLuc cells, and 7 miRNAs were confirmed to also sensitize PC3-MLuc cells (Fig. 2A). Four miRNAs, miR-890, miR-744-3p, miR-32-3p and miR-130b-5p demonstrated equal or greater radiosensitization efficiency, when compared to the DNAPK siRNA positive control, in both cells. The radiation sensitizing potential of these miRNAs was further quantified by clonogenic survival assays (Fig. 2B, and Fig. 11). The dose-modifying factor (DMF) for each miRNA was calculated as the ratio of IR dose required to cause 90% cell death by control miRNA versus the dose required to cause 90% cell death by the candidate miRNAs. The two most potent miRNAs, miR-890-5p and miR-744-3p, achieved $DMF_{0.1}$ of 1.52 and 1.46, respectively (Fig. 2B). It was anticipated that these miRNAs function through targeted regulation of DNA repair processes.

[0135] miR-890-5p and miR-744-3p radiosensitize cells through inhibition of DNA repair

[0136] DNA repair pathways play an important role in cellular response to IR. A hallmark of DNA DSB detection and repair is phosphorylation of H2AX. Following DNA repair, these γ -H2AX foci are resolved by phosphatase activity (Firsanov DV, Solovjeva LV, Svetlova MP (2011) *Clin Epigenetics* 2(2):283-297.). The influence of miR-890-5p and miR-744-3p on the formation and resolution of γ -H2AX foci was examined over 24 h using irradiated (4 Gy)

DU145 cells. Within 1 h of IR, γ -H2AX foci formation was visible in all treatment groups (Fig. 3A). Within 8 h, the control treated cells had resolved most of the γ -H2AX foci. However, the radiation sensitizing miRNAs, miR-890-5p and miR-744-3p, significantly delayed γ -H2AX resolution over the 24 h time period (Fig. 3A and 3B).

[0137] To more directly study DNA damage and repair, irradiated cells were examined by the single cell gel electrophoresis comet assay. As above, DU145 cells were transfected with control or radiation sensitizing miRNAs and then treated with 4 Gy of IR 48 h post transfection. Within 4 h of IR, DNA comet tails moments were significantly extended in cells transfected with miR-890-5p and miR-744-3p, when compared to cells transfected with control miRNA (Fig. 3C and 3D). Collectively these data support that miR-890-5p and miR-744-3p inhibited DNA repair processes, which likely contributed to the radiation sensitization phenotype.

[0138] miR-890-5p and miR-744-3p regulate multiple components of DDR pathways

[0139] Several DDR genes were previously characterized as potent radiation sensitizing targets, including DNAPK, MAD2L2, BRCA2, NBN, RAD23B and RAD54L (Ni X, et al. (2011) J Clin Invest 121(6):2383-2390.). These genes were examined to determine whether they may be direct targets of the identified radiation sensitizing miRNAs by *in silico* analysis (Table 4).

Table 4. Radiation sensitizing miRNAs predicted to target radiation sensitizing DDR pathway genes using *in silico* analysis, microRNA.org.

	DNAPK	MAD2L2	BRCA2	NBN	RAD23B	RAD54L
miR-130b*	-0.0444				-0.0029	-0.4047
miR-890		-0.5108		-0.1413	-0.0121	
miR-744*			-0.1147	-0.0084	-0.7604	
miR-32*			-0.1559	-0.6390	-0.0488	

The bolded values corresponding to the miRNAs with a mirSVR score < -0.5.

miR-890-5p and miR-744-3p were predicted to target two of these genes, MAD2L2 and RAD23B, respectively, with mirSVR Scores < -0.5, indicating a high probability of target gene down-regulation (Betel D, Koppal A, Agius P, Sander C, Leslie C (2010) Genome Biol 11(8):R90.). Transfection of miR-890-5p resulted in reduced MAD2L2 protein levels in multiple prostate cancer cell lines, as detected by western blot (Fig. 4A). As also predicted, miR-744-3p transfection resulted in reduced RAD23B protein levels (Fig. 4A). The 3'UTR regions of the respective genes were then subcloned downstream of firefly luciferase to generate miRNA specific reporters (Fig. 4B).

[0140] The respective 3'UTR luciferase activities of MAD2L2 and RAD23B were significantly down-regulated by miR-890-5p and miR-744-3p transfection (Fig. 4C). Mutation of the corresponding miRNA seed binding sites ablated miRNA mediated suppression (Fig. 4C), indicating direct miRNA regulation of these genes.

[0141] Because a single miRNA has the potential to regulate the expression of multiple genes (Lewis BP, Burge CB, Bartel DP (2005) Cell 120(1):15-20.), it is anticipated that miR-890-5p and miR-744-3p may regulate additional DDR pathway components. *In silico* analysis using microRNA.org predicted several additional DDR pathway targets for miR-890-5p or miR-744-3p, each with high mirSVR scores (Table 5).

Table 5. Potential DDR pathway genes predicted to be targeted by miR-890-5p or miR-744-3p using *in silico* analysis, microRNA.org, and corresponding mirSVR scores.

DDR pathway genes	miRNA	mirSVR score
WEE1	miR-890	-1.1805
XPC	miR-890	-0.9251
MAD2L2	miR-890	-0.5108
KU80	miR-890	-0.4843
XLF	miR-744*	-0.8632
RAD23B	miR-744*	-0.7604
MCL1	miR-744*	-0.6699

Western blot analyses confirmed that miR-890-5p transfection also reduced the target genes WEE1, XPC, and KU80 (Fig. 5A and C). In addition, miR-744-3p transfection reduced the levels of XLF and MCL1 (Fig. 5B and D).

[0142] Analysis of miR-890-5p and its multiple targets on cellular sensitivity to IR

[0143] The multifunctional nature of the identified miRNAs suggests that they may be more potent radiation sensitizing agents than rationally designed siRNAs engineered to target a single DDR gene. When cells were treated with an equal dose of MAD2L2-targeting siRNA or miR-890-5p miRNA (10 nM), the expression of MAD2L2 was most strongly down-regulated by the siRNA (Fig. 6A). However, miR-890-5p transfection resulted in greater radiation sensitizing efficacy, when compared to MAD2L2 siRNA, at multiple dose levels (Fig. 6B). To further study whether miR-890-5p radiation sensitization was dependent upon MAD2L2

silencing, cells were co-transfected with the miR-890-5p mimetic and MAD2L2 siRNA (Fig. 6B). The addition of miR-890-5p to MAD2L2 siRNA resulted in greater IR sensitization at all doses studied (Fig. 6B), including at higher doses where no additional MAD2L2 knock-down was detected (Fig. 6A). This supports that miR-890-5p functions as a radiation sensitizer by targeting additional genes beyond MAD2L2. The miR-890-5p target WEE1, was not observed to be further reduced by the knock-down of MAD2L2 mRNA (Fig. 12), indicating that miR-890-5p regulates these genes independently. The calculated IC_{50} of MAD2L2 siRNA, miR-890-5p and combined MAD2L2 siRNA and miR-890-5p were 0.49 nM, 0.36 nM and 0.15 nM, respectively (Fig. 6C).

[0144] miR-890-5p mimetic sensitizes established prostate cancer tumors to IR

[0145] In view of the potent and multifunctional nature of miR-890-5p radiation sensitization *in vitro*, it was determined whether a miR-890-5p mimetic could enhance the therapeutic effect of IR *in vivo*. Established subcutaneous DU145 prostate tumors were directly treated with miR-890-5p or control miRNA mimetics, in liposomal formulation, with a single intratumoral administration. Two days after injection, one cohort of tumors was irradiated with a single dose of 6 Gy, while the other cohort was not irradiated. A final control cohort was treated with PBS only. Tumor volume was evaluated over 35 days and the time to tumor volume quadrupling was calculated.

[0146] In the absence of irradiation, the tumor grew comparably with miR-890, control miRNA, or PBS treatment (Fig. 7A and Figs. 13A-E). On the other hand, after irradiation, the tumor volume of miR-890-5p treated mice was significantly reduced when compared to the miRNA control. The miR-890-5p mimetic significantly delayed the time to tumor quadrupling of irradiated mice by 14 days, when compared to the control miRNA (Fig. 7B). These results support the use of miR-890-5p as a potent radiation sensitizing agent.

EQUIVALENTS

[0147] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[0148] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application

was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[0149] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A composition for increasing sensitization to ionizing radiation (IR) comprising an miRNA; miRNA mimetic, activator of miRNA, or mixture thereof.
2. The composition of claim 1, wherein the miRNA comprises miR-744.
3. The composition of claim 2, wherein the miRNA comprises miR-744-3p or miR-744-5p.
4. The composition of claim 3, wherein the miR-744-3p comprises SEQ ID NO: 734.
5. The composition of claim 1, wherein the miRNA comprises miR-890.
6. The composition of claim 5, wherein the miRNA comprises miR-890-5p or miR-890-3p.
7. The composition of claim 6, wherein miR-890-5p comprises SEQ ID NO: 764.
8. The composition of claim 1, wherein the activator of miRNA activates endogenous miR-890-5p or miR-744-3p when administered to a patient.
9. The composition of claim 1, wherein the miRNA mimetic, mimics miR-890-5p or miR-744-3p.
10. The composition of claim 1, wherein the composition further comprises a chemotherapeutic agent.
11. The composition of claim 1, wherein the composition is administered 1-5 days prior to treatment with IR.
12. The composition of claim 11, wherein the dose of IR comprises between 0 Gy and 30 Gy in a single fraction of externally applied radiation.
13. The composition of claim 11, wherein the dose of IR comprises between 0 Gy and 20 Gy per fraction in multiple fractions by externally applied radiation.
14. The composition of claim 11, wherein the dose of IR comprises low dose rate brachytherapy dosing of 0 – 2 Gy/minute.
15. The composition of claim 11, wherein the dose of IR comprises high dose rate brachytherapy dosing of 2 – 20 Gy/minute.
16. A method of increasing sensitivity to ionizing radiation (IR) therapy or chemotherapy in a patient in need thereof, the method comprising:
administering to the patient in need thereof a composition comprising an miRNA, miRNA mimetic, activator of miRNA, or mixture thereof.
17. The method of claim 16, wherein the miRNA comprises miR-744.

18. The method of claim 17, wherein the miRNA comprises miR-744-3p or miR-744-5p.
19. The method of claim 18, wherein the miR-744-3p comprises SEQ ID NO: 734.
20. The method of claim 16, wherein the miRNA comprises miR-890.
21. The method of claim 20, wherein the miRNA comprises miR-890-5p or miR-890-3p.
22. The method of claim 21, wherein miR-890-5p comprises SEQ ID NO: 764.
23. The method of claim 16, wherein the composition is administered prior to IR treatment.
24. The method of claim 23, wherein the composition is administered 1-5 days prior to treatment with IR.
25. The method of claim 23, wherein the dose of IR comprises between 0 Gy and 30 Gy in a single fraction of externally applied radiation.
26. The method of claim 23, wherein the dose of IR comprises between 0 Gy and 20 Gy per fraction in multiple fractions by externally applied radiation.
27. The method of claim 23, wherein the dose of IR comprises low dose rate brachytherapy dosing of 0 – 2 Gy/minute.
28. The method of claim 23, wherein the dose of IR comprises high dose rate brachytherapy dosing of 2 – 20 Gy/minute.
29. The method of claim 16, wherein the composition is co-administered with a chemotherapeutic agent.
30. The method of claim 16, wherein the patient in need thereof is a patient with cancer or tumors of the skin, brain and other central nervous system sites, head, neck, muscle/sarcoma, bone, lung, esophagus, stomach, pancreas, colon, rectum, uterus, cervix, vagina, vulva, penis, breast, kidney, prostate, bladder, or thyroid.
31. The method of claim 16, wherein the patient in need thereof is a patient with prostate cancer.
32. A method of increasing sensitivity to IR therapy or chemotherapy in a tumor cell, the method comprising:
contacting the tumor cell with a composition comprising an miRNA, miRNA mimetic, activator of miRNA, or mixture thereof,
thereby increasing sensitivity to IR therapy or chemotherapy.

FIG. 1A

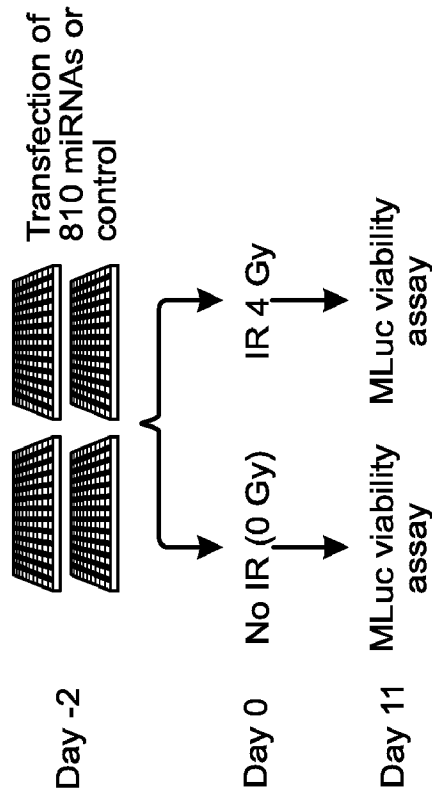


FIG. 1B

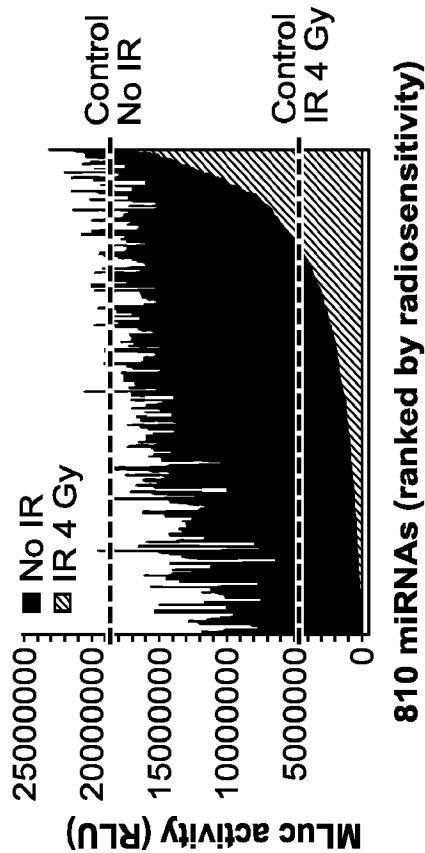


FIG. 1C

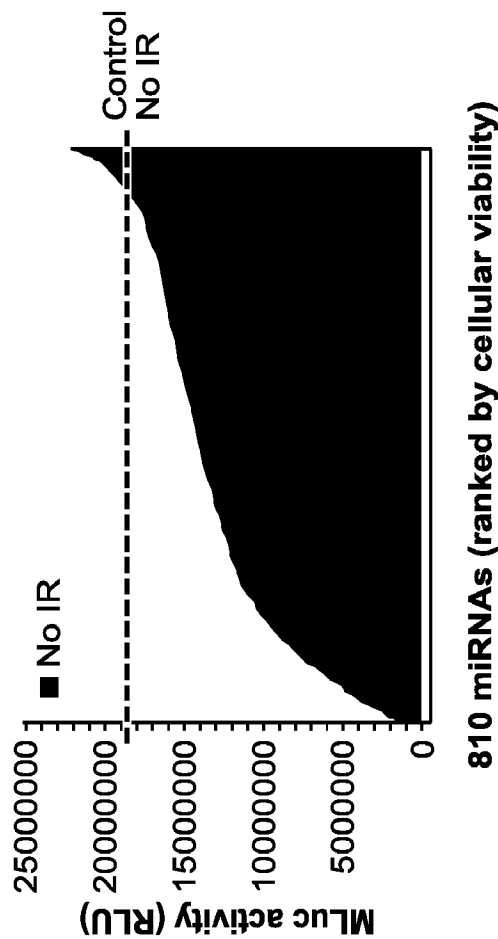
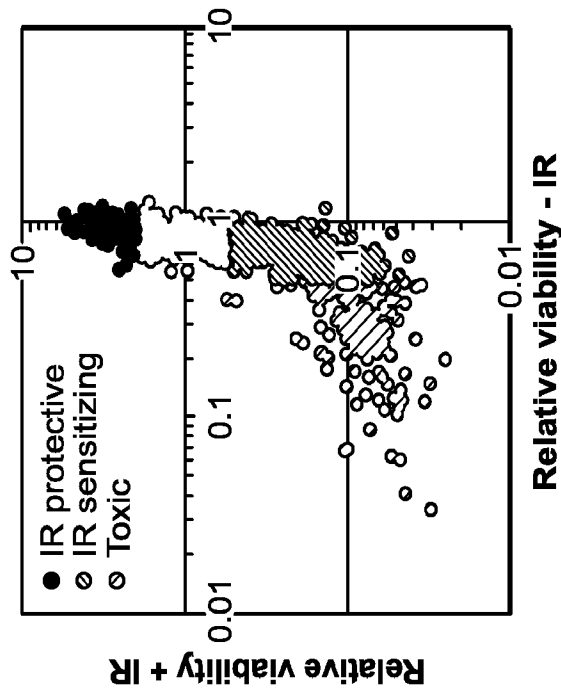
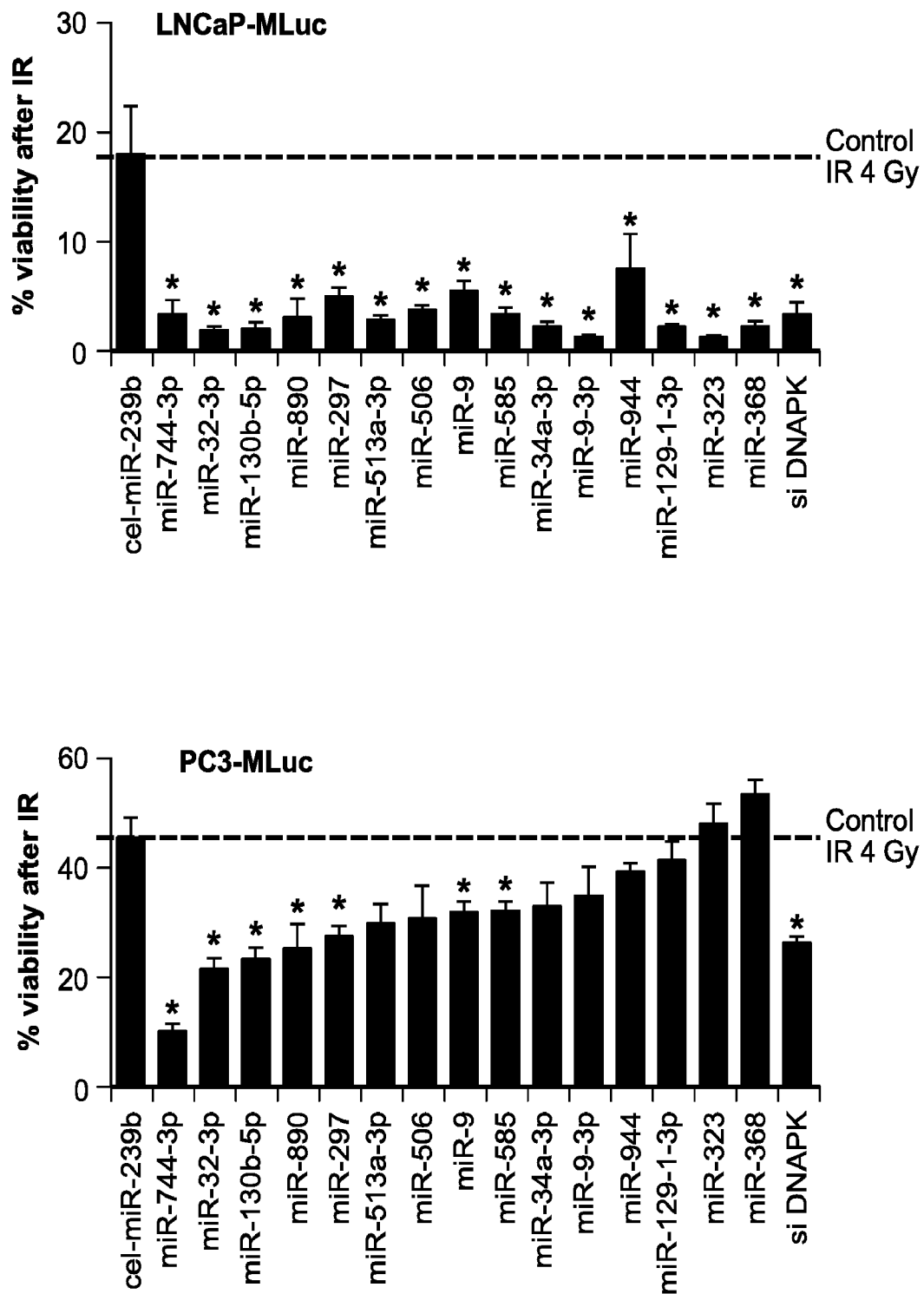


FIG. 1D



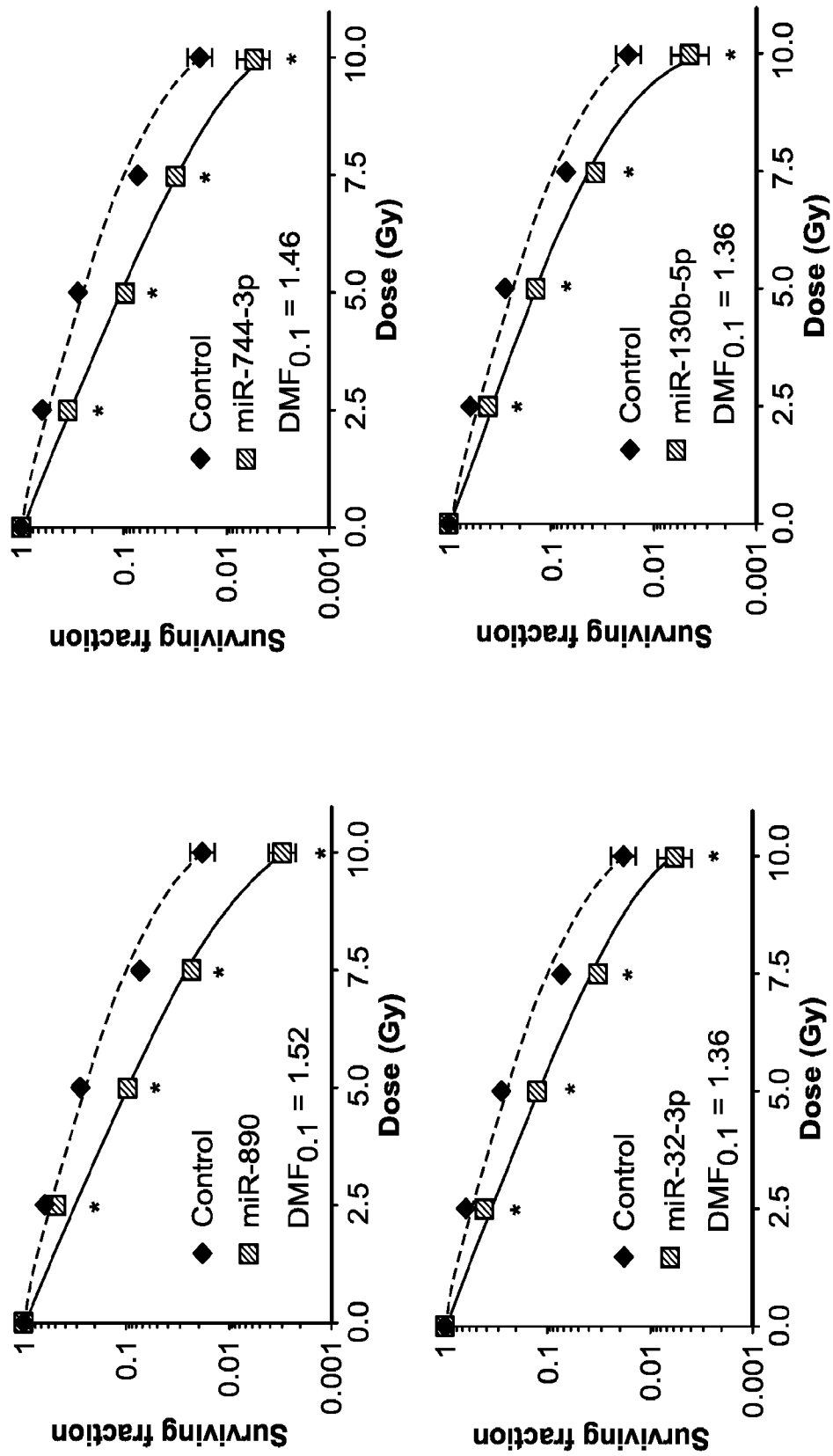
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FIG. 2A



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FIG. 2B



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FIG. 3A

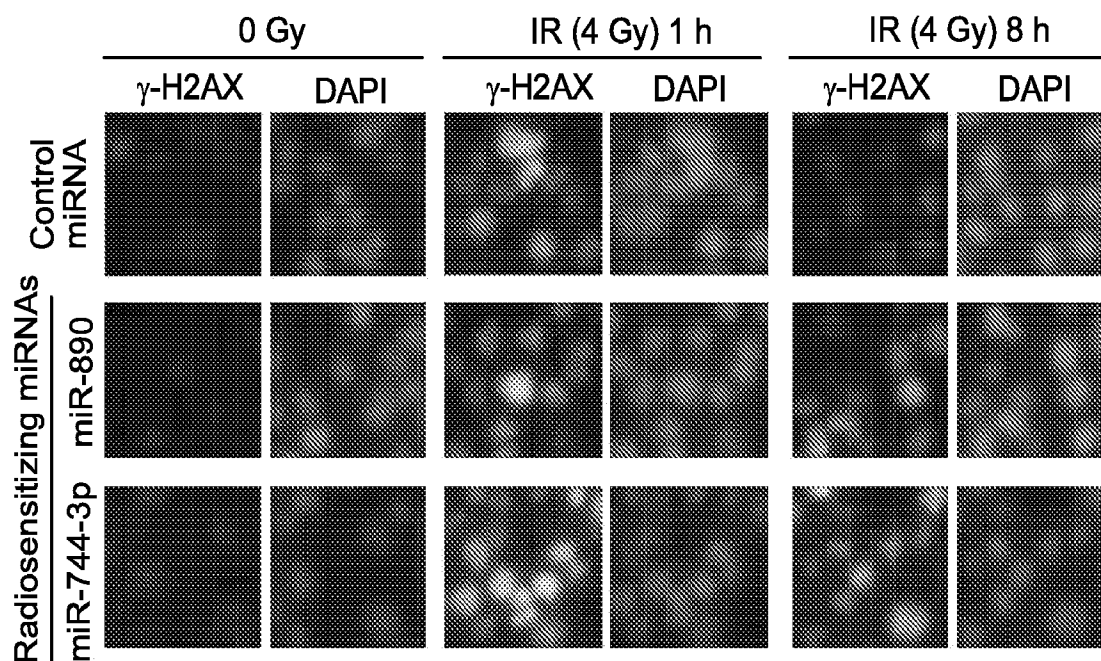
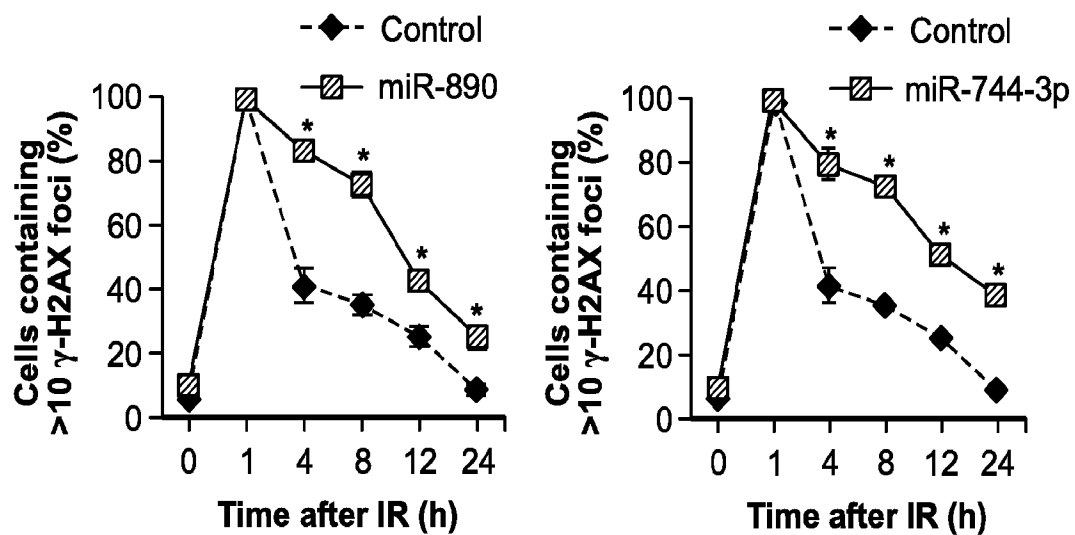


FIG. 3B



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FIG. 3C

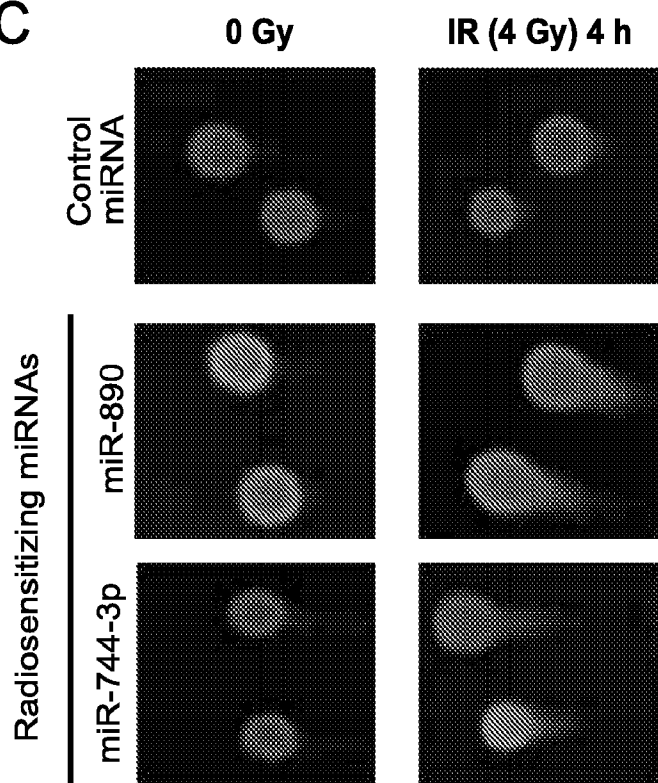


FIG. 3D

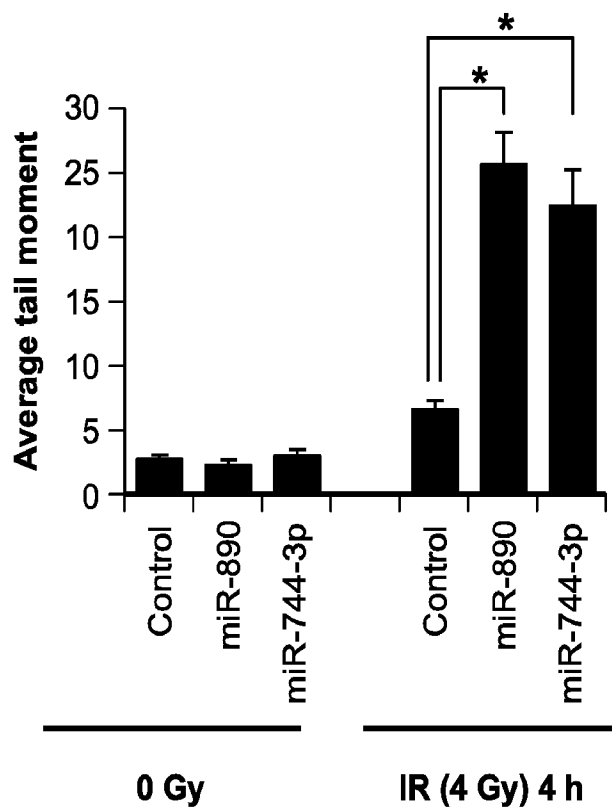


FIG. 4A

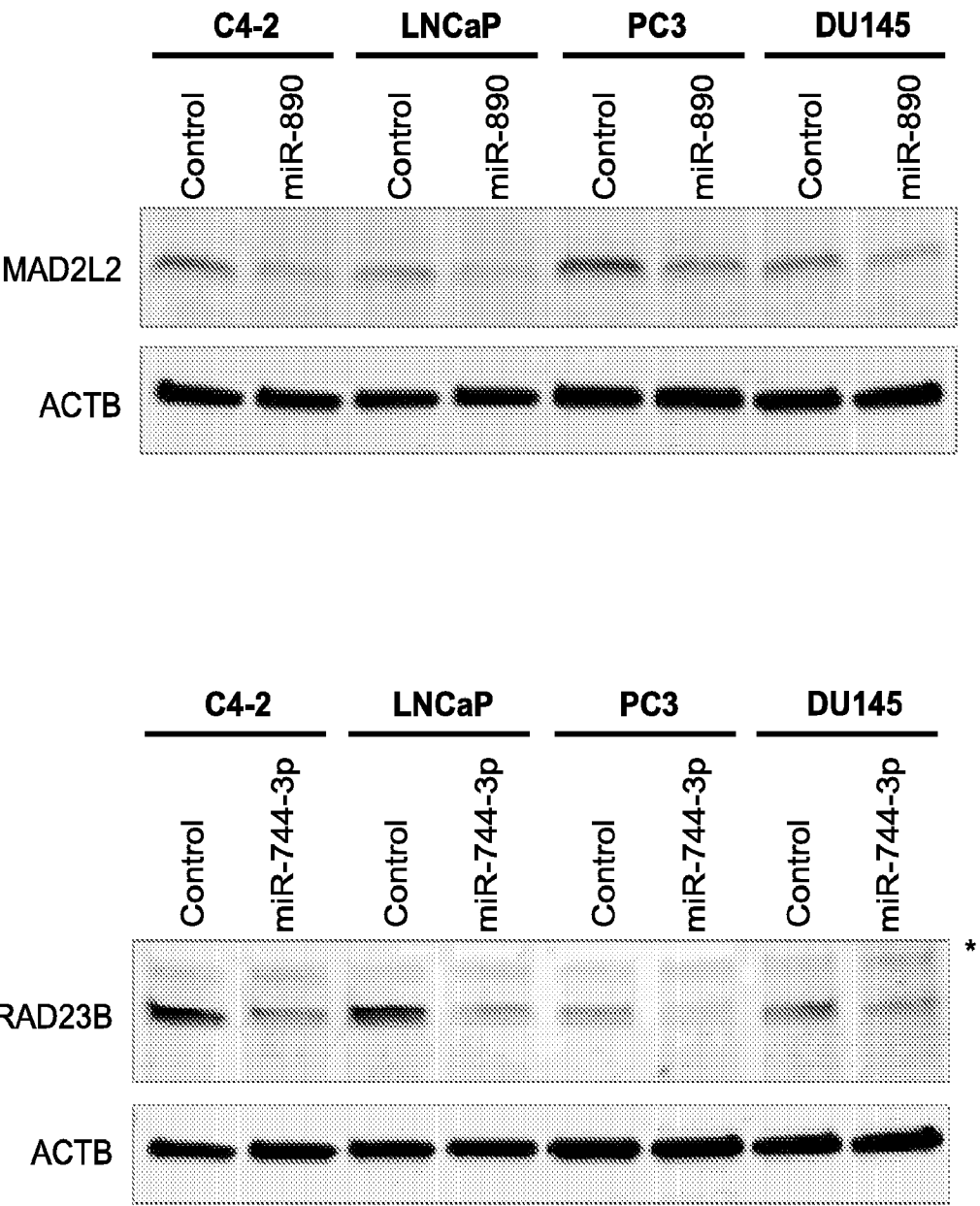


FIG. 4B

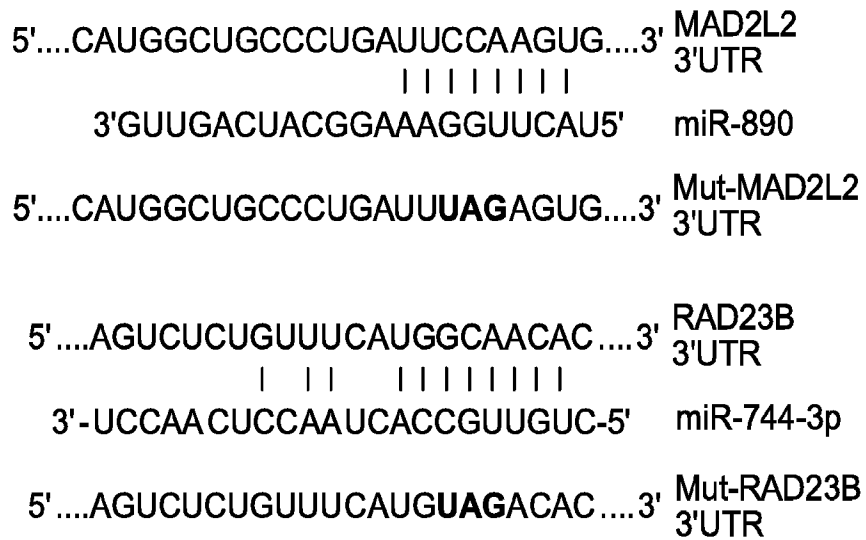
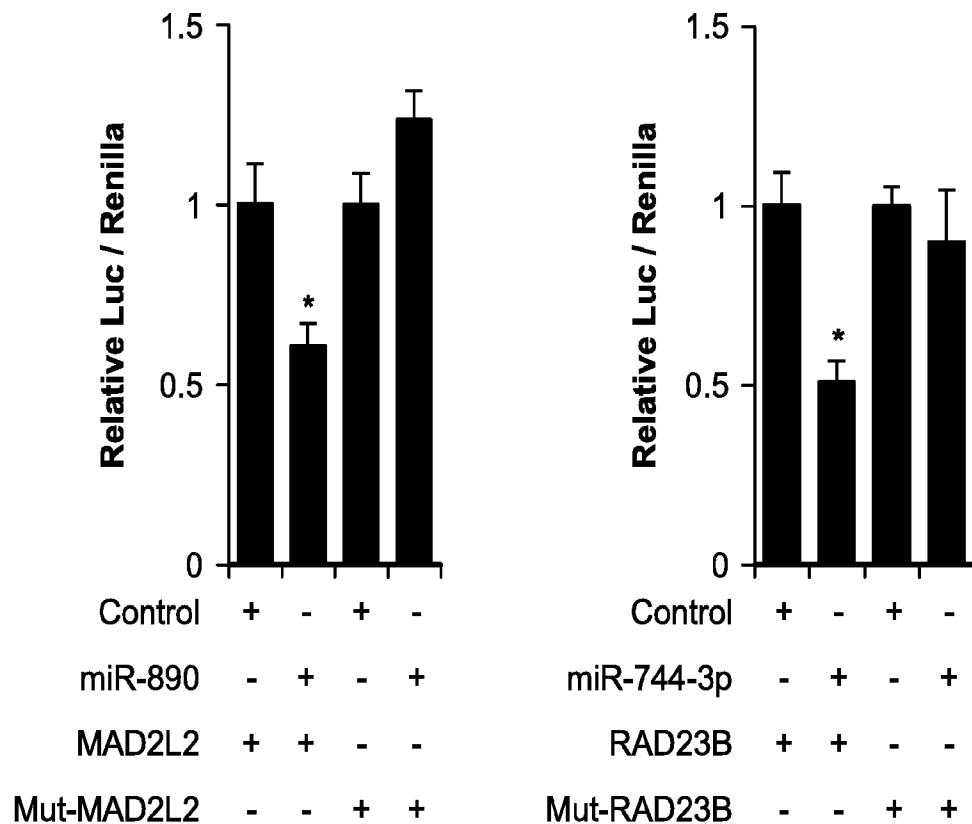


FIG. 4C



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FIG. 5A

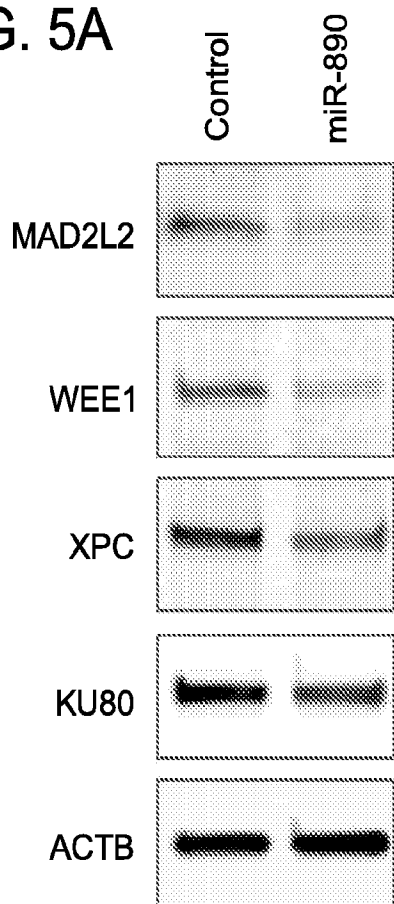


FIG. 5B

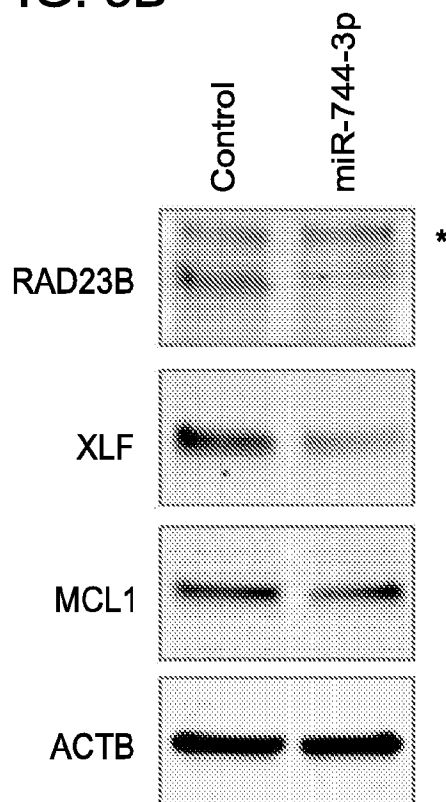


FIG. 5C

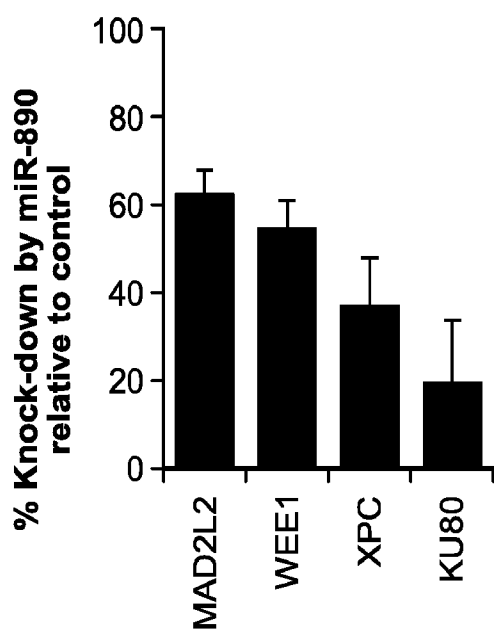


FIG. 5D

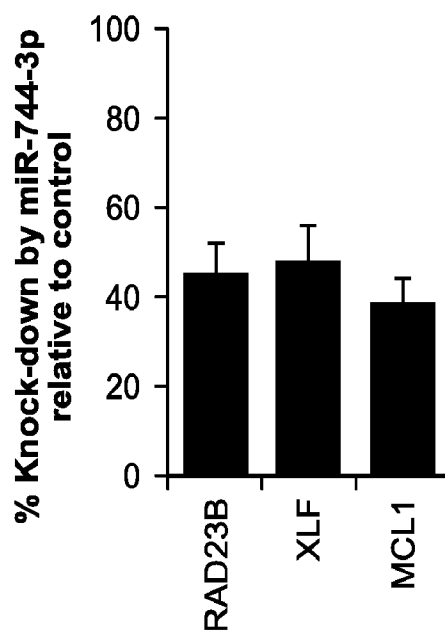


FIG. 6A

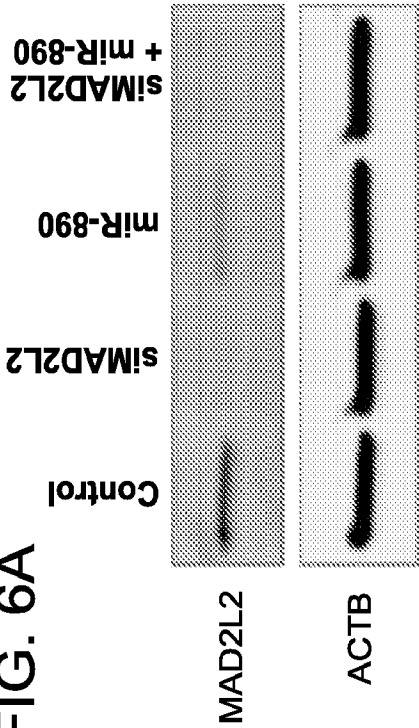


FIG. 6C

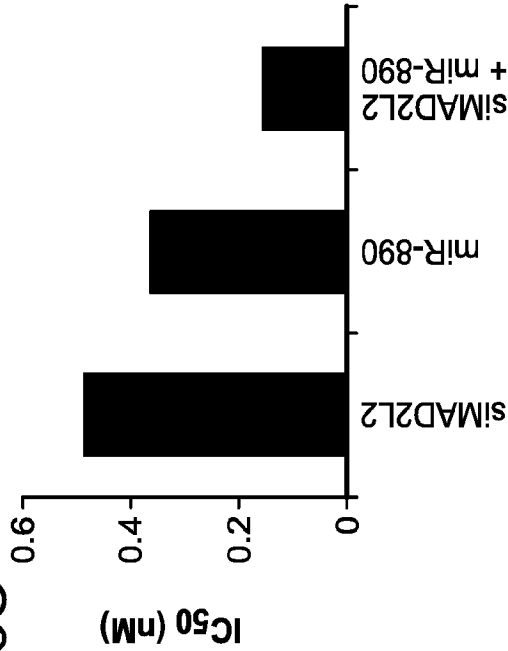
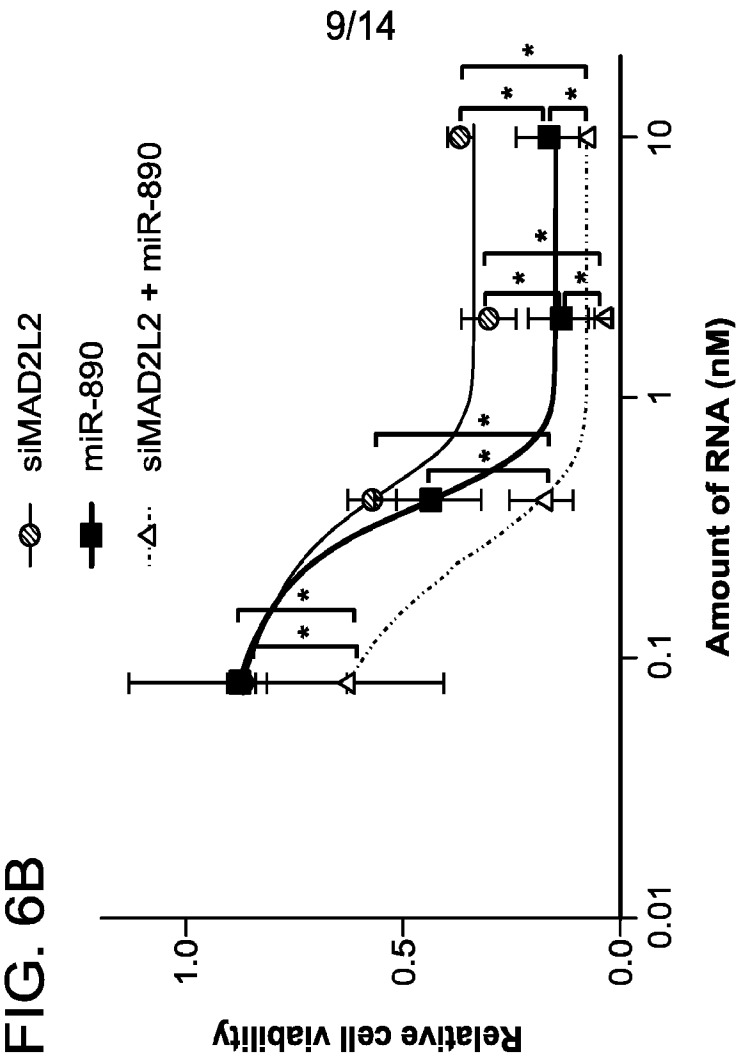


FIG. 6B



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FIG. 7A

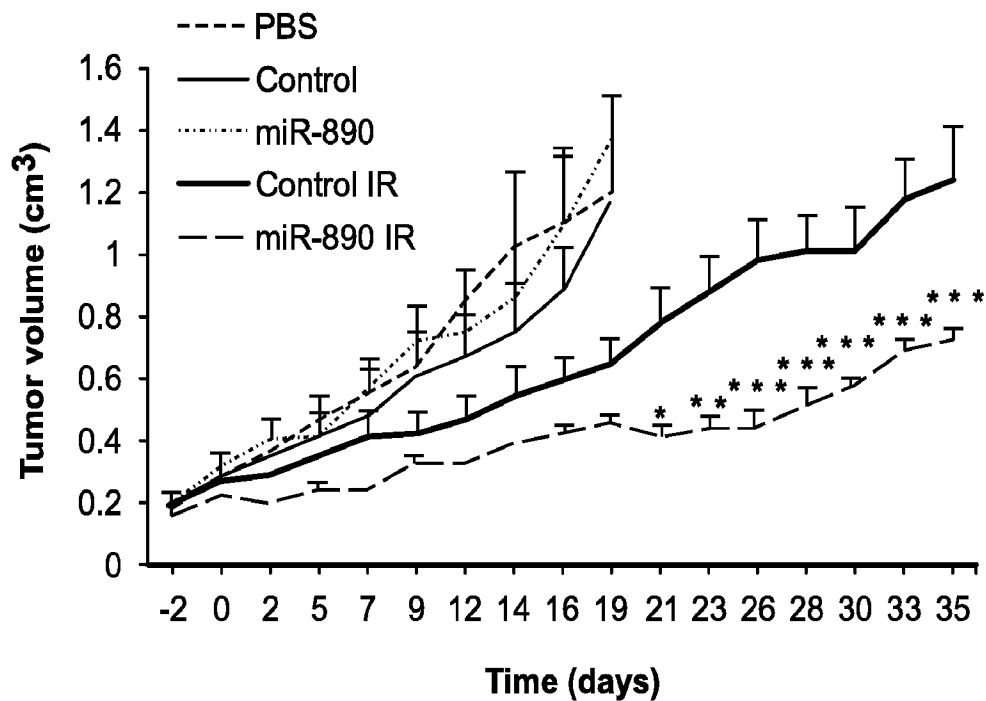
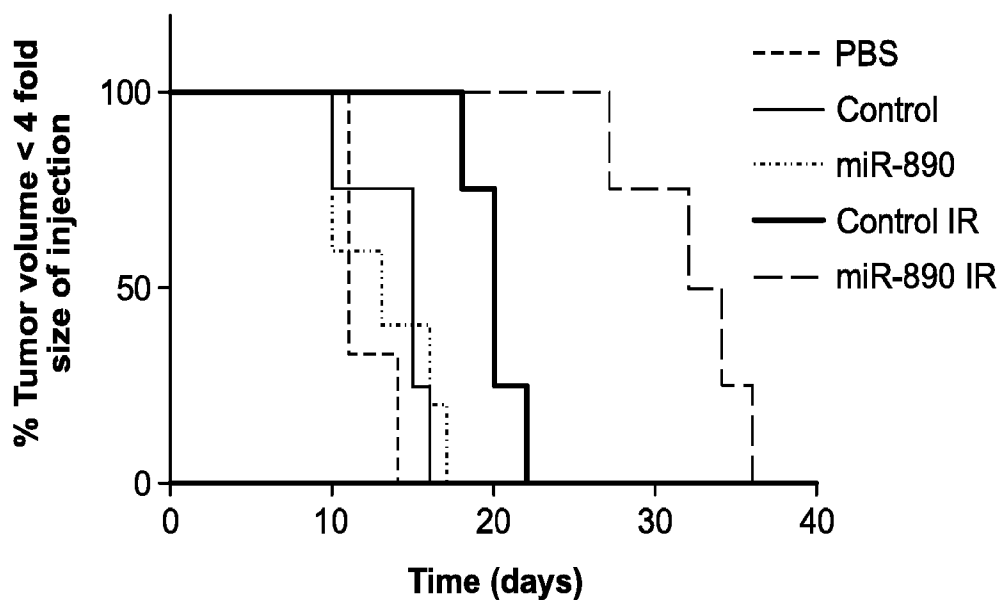


FIG. 7B



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FIG. 8A

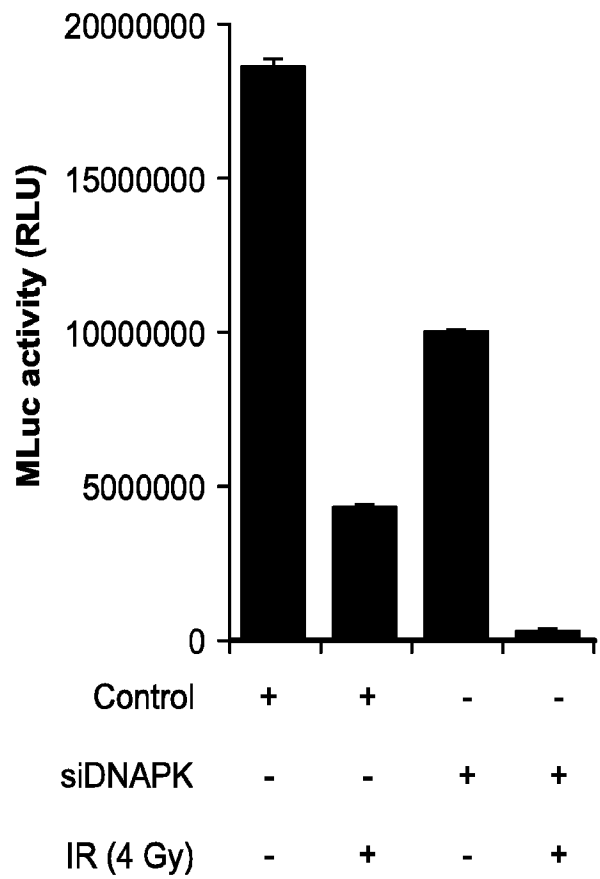


FIG. 8B

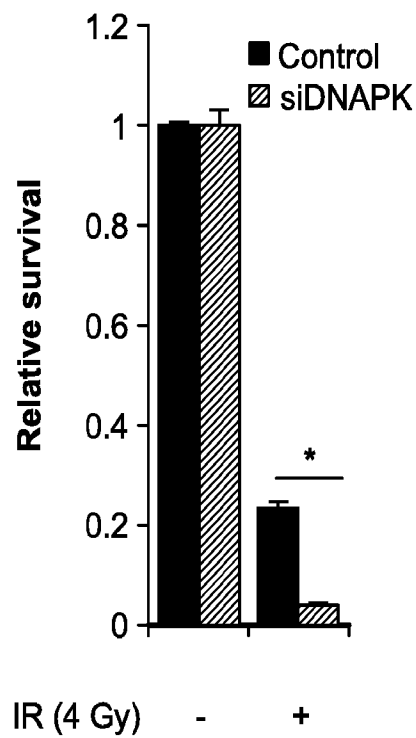


FIG. 9A

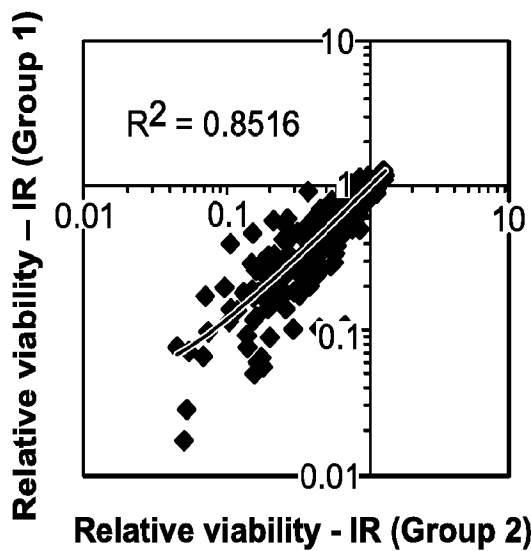


FIG. 9B

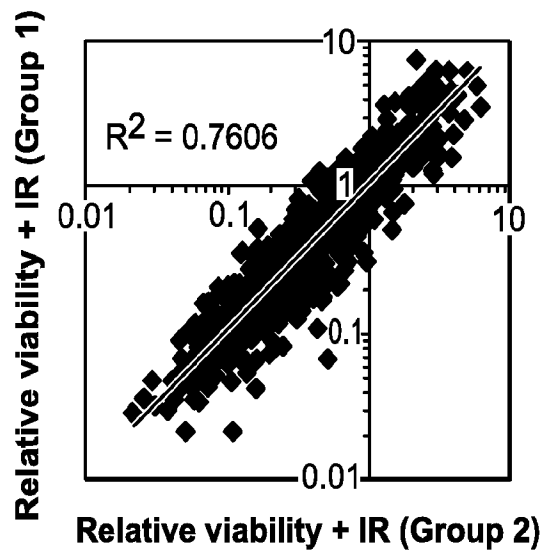
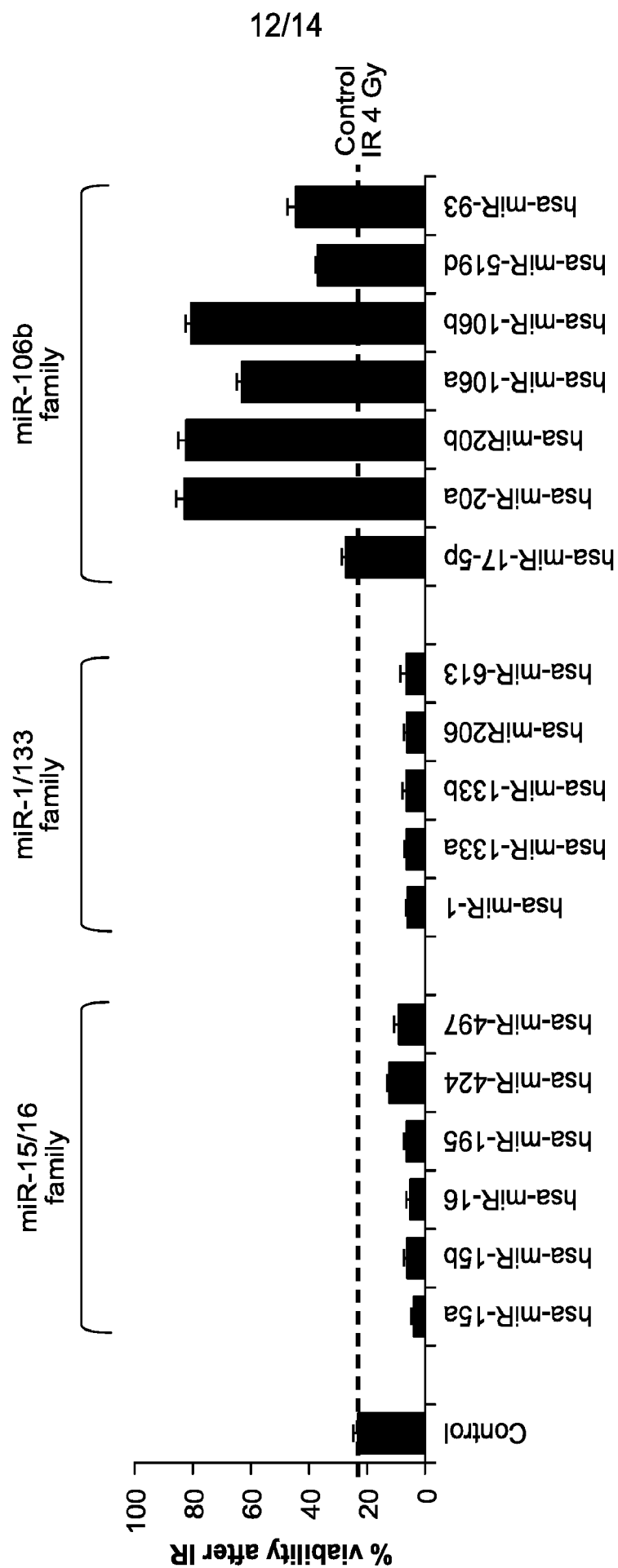


FIG. 10



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FIG. 11

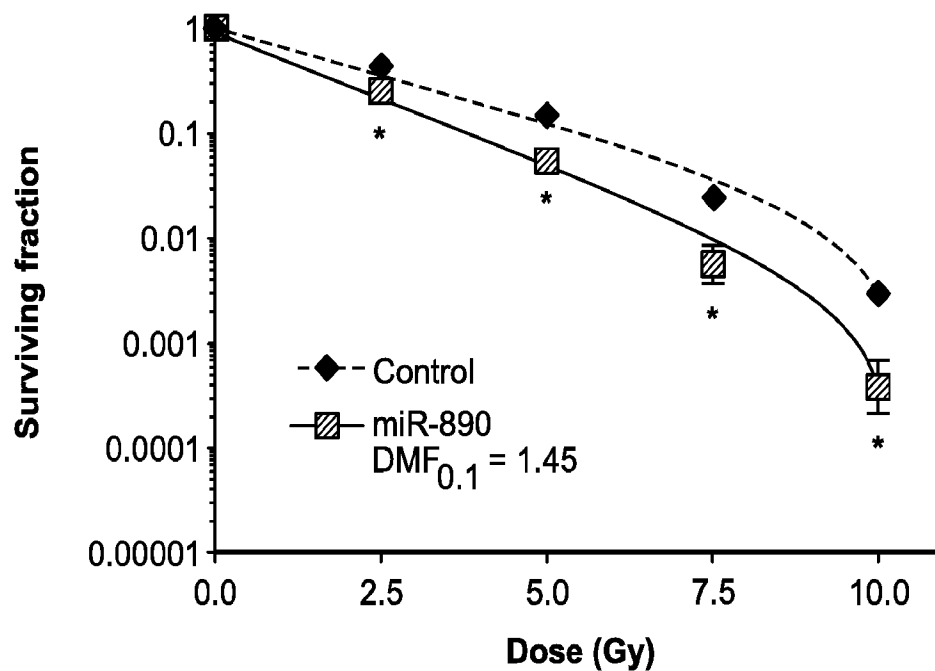


FIG. 12

Control	+	+	+	+	-	-	-	-
miR-890	-	-	-	-	+	+	+	+
siMAD2L2 (nM)	0	0.1	0.5	2	0	0.1	0.5	2

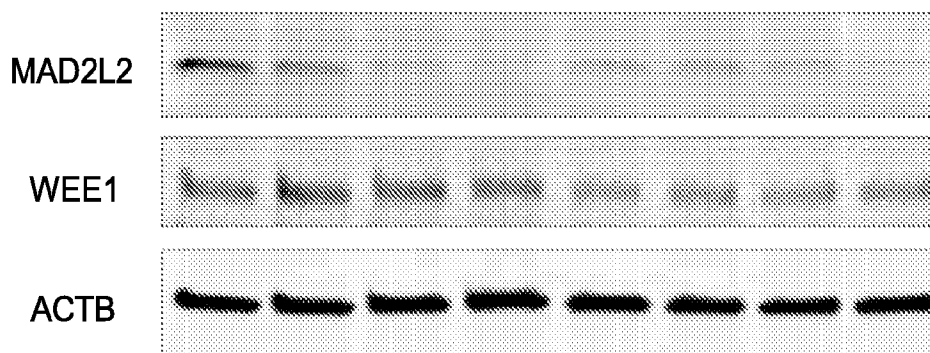


FIG. 13A

PBS

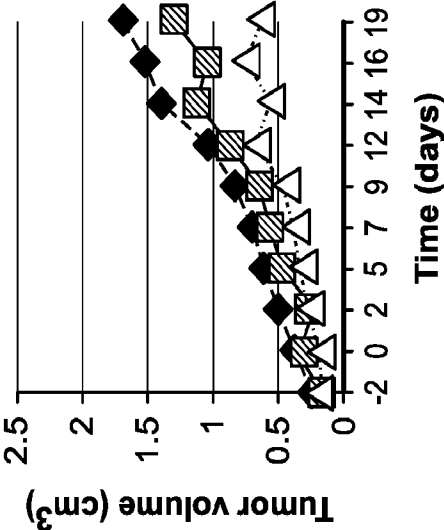


FIG. 13B

Control

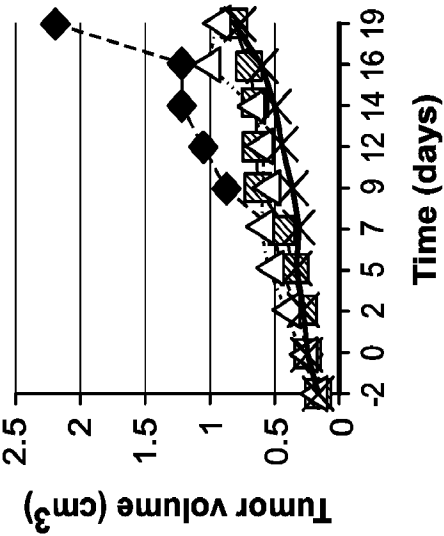


FIG. 13C

miR-890

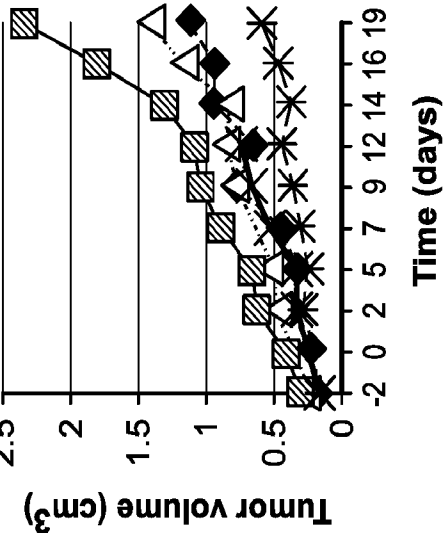


FIG. 13D

Control IR

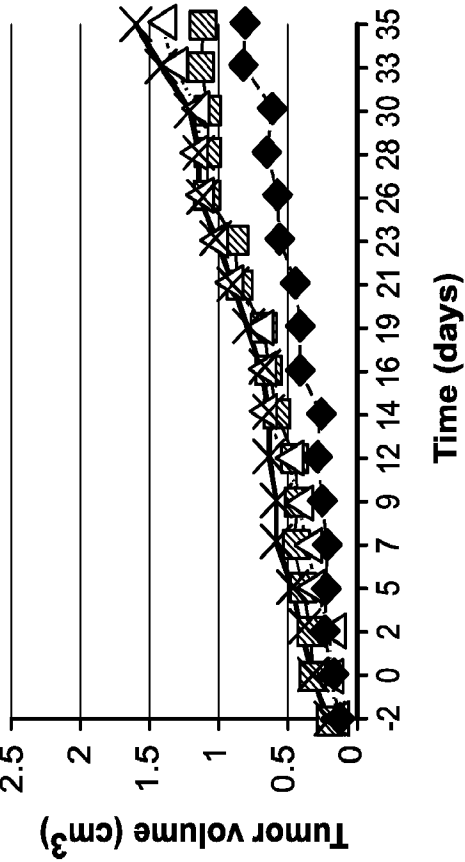


FIG. 13E

miR-890 IR

