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(54) **Title:** METHOD FOR PREDICTING CARDIOTOXICITY RISK IN CANCER PATIENTS RECEIVING ANTHRACYCLINES CHEMOTHERAPY

(57) **Abstract:** The present invention refers to an in vitro method for predicting cardiotoxicity risk in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy based on the determination of the expression levels of a combination of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, in a biological sample isolated from the patient. The present invention also refers to said set of 10 circulating miRNAs for its use as biomarker of prediction of cardiotoxicity risk in cancer patients receiving, or susceptible to receive, anthracyclines chemotherapy. Finally, a method for the prevention of cardiotoxicity, in patients receiving or susceptible to receive anthracyclines chemotherapy, that comprises modulating the expression levels of the set of said 10 circulating miRNAs is contemplated.



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**METHOD FOR PREDICTING CARDIOTOXICITY RISK IN CANCER PATIENTS
RECEIVING ANTHRACYCLINES CHEMOTHERAPY**

DESCRIPTION

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Field of the invention

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The present invention relates generally to the field of Oncology and Toxicology. Particularly, the invention relates to a method for predicting cardiotoxicity risk in cancer patients receiving, or susceptible to receive, anthracyclines chemotherapy. The method is based on the analysis of the expression levels of a set of 10 circulating miRNAs.

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Background of the invention

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Anthracyclines are well-established and effective anti-neoplastic drugs currently used alone or in combination with other anti-mitotic agents for the treatment of a wide variety of tumors including breast cancer (*Palmieri C, Krell J, James CR, et al. Rechallenging with anthracyclines and taxanes in metastatic breast cancer. Nat Rev Clin Oncol 2010; 7(10): 561-741*). However, its implementation is related with several collateral effects, being cardiotoxicity the most severe. Usually the first symptoms appear within the first year of administration of the last dose, but it may occur even after 6-10 years after administration (*Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015; 131(22): 1981-82*).

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Anthracyclines induced cardiotoxicity (AC) is considered acute if occurs shortly after its administration (*Cardinale D. et al; Takemura G, Fujiwara H. Doxorubicin-induced cardiomyopathy from the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007; 49(5): 330-52*). However, since the toxicity of anthracyclines is cumulative, the most common type of AC occurs several years after the treatment what is known as chronic cardiotoxicity. Since the heart is a post-mitotic organ, once the myocardium is damaged the deterioration of heart function is commonly progressive. Early assessment for cardiac toxicity following anthracycline treatment could aid to perform

a more precise risk stratification of patients who may benefit from more frequent surveillance cardiac function.

miRNAs have been involved in pivot biological processes such as drug resistance
(Ahmad N, Haider S, Jagannathan S, Anaissie E, Driscoll JJ. *MicroRNA theragnostics for the clinical management of multiple myeloma. Leukemia* 2014; 28(4): 732-8),
cellular damage or cancer (Allegra A, Alonci A, Campo S, et al. *Circulating microRNAs: new biomarkers in diagnosis, prognosis and treatment of cancer (review). Int J Oncol* 2012; 41(6): 1897-912). These molecules are a small class of
single trans noncoding RNAs between 20-25 nucleotides that control expression of
mRNAs at the post-transcriptional level by targeting the 3'untranslated region of
mRNA transcripts (Ambros V. *The functions of animal microRNAs. Nature* 2004; 431(7006): 350-5). They can cleave complementary messenger mRNA targets and
diminish the translation of partially complementary targets (Kim VN. *MicroRNA biogenesis: coordinated cropping and dicing. Nat Rev Mol Cell Biol* 2005; 6(5): 376-
85). These short molecules have high specificity and many of them have a tissue
specific expression (Latronico MV, Catalucci D, Condorelli G. *Emerging role of microRNAs in cardiovascular biology. Circ Res* 2007; 101(12): 1225-36). Due to its
high stability in plasma and serum and easy detection they have been used as
biomarkers in different pathologies including cancer (Hamam R, Hamam D, Alsaleh
KA, et al. *Circulating microRNAs in breast cancer: novel diagnostic and prognostic biomarkers. Cell Death Dis* 2017; 8(9): e3045) and cardiac diseases (Gilad S, Meiri
E, Yogev Y, et al. *Serum microRNAs are promising novel biomarkers. PLoS One* 2008; 3(9): e3148; Mitchell PS, Parkin RK, Kroh EM, et al. *Circulating microRNAs as
stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A* 2008; 105(30): 10513-8; Schulte C, Zeller T. *microRNA-based diagnostics and therapy in
cardiovascular disease-Summing up the facts. Cardiovasc Diagn Ther* 2015; 5(1): 17-
36) and specific patterns of circulating miRNAs have been associated with heart
failure (Tijssen AJ, Creemers EE, Moerland PD, et al. *MiR423-5p as a circulating
biomarker for heart failure. Circ Res* 2010; 106(6): 1035-9) and myocardial infarction
(Wang GK, Zhu JQ, Zhang JT, et al. *Circulating microRNA: a novel potential
biomarker for early diagnosis of acute myocardial infarction in humans. Eur Heart J* 2010; 31(6): 659-66). This circulating miRNAs were found stable under unfavourable
conditions as high or low PH, boiling and multiple freeze-thaw cycles (Mitchell PS,

Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci U S A* 2008; 105(30): 10513-8; Lawrie CH, Gal S, Dunlop HM, et al. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br J Haematol* 2008; 141(5): 672-5) suggesting that circulating miRNAs are protected from degradation.

Currently there are few studies linking treatment with anthracyclines and the detection of circulating microRNAs. Using induced pluripotent stem cells (iPSC) derived cardiomyocytes (CM) treated with Doxorubicin it was shown a deregulation of miR-187-3p, miR-182-5p, miR-486-3p, miR-486-5p, miR-34a-3p, miR-4423-3p, miR-34c-3p, miR-34c-5p and miR-1303 in treated cells in comparison to non-treated controls (Chaudhari U, Nemade H, Gaspar JA, Hescheler J, Hengstler JG, Sachinidis A. MicroRNAs as early toxicity signatures of doxorubicin in human-induced pluripotent stem cell-derived cardiomyocytes. *Arch Toxicol* 2016; 90(12): 3087-98). In vivo, it was reported the usefulness of miR-208 (Calvano J, Achanzar W, Murphy B, et al. Evaluation of microRNAs-208 and 133a/b as differential biomarkers of acute cardiac and skeletal muscle toxicity in rats. *Toxicol Appl Pharmacol* 2015; Nishimura Y, Kondo C, Morikawa Y, et al. Plasma miR-208 as a useful biomarker for drug-induced cardiotoxicity in rats. *J Appl Toxicol* 2015; 35(2): 173-80), miR-133a/b, miR146a (Horie T, Ono K, Nishi H, et al. Acute doxorubicin cardiotoxicity is associated with miR-146a-induced inhibition of the neuregulin-ErbB pathway. *Cardiovasc Res* 2010; 87(4): 656-64) and miR-34a (Desai VG, J CK, Vijay V, et al. Early biomarkers of doxorubicin-induced heart injury in a mouse model. *Toxicol Appl Pharmacol* 2014; 281(2): 221-9) as useful biomarkers for drug-induced cardiotoxicity in rats. Recently, the levels of several miRNAs were analyzed in blood of childhood patients treated with anthracyclines and determined that only miR-29b and miR-499 significantly correlated with cumulative anthracycline dosage shortly after infusion (Leger KJ, Leonard D, Nielson D, de Lemos JA, Mammen PP, Winick NJ. Circulating microRNAs: Potential Markers of Cardiotoxicity in Children and Young Adults Treated With Anthracycline Chemotherapy. *J Am Heart Assoc* 2017; 6(4)). In this context, some molecular prognostic classifiers based on miRNA detection have been developed for cardiac induced toxicity after treatment with Trastuzumab (Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc* 2014; 3(1): e000472) or

anthracyclines (Leger KJ, Leonard D, Nielson D, de Lemos JA, Mammen PP, Winick NJ. *Circulating microRNAs: Potential Markers of Cardiotoxicity in Children and Young Adults Treated With Anthracycline Chemotherapy*. *J Am Heart Assoc* 2017; 6(4); Leger K, Slone T, Lemler M, et al. *Subclinical cardiotoxicity in childhood cancer survivors exposed to very low dose anthracycline therapy*. *Pediatr Blood Cancer* 2015; 62(1): 123-7; Lipshultz SE, Diamond MB, Franco VI, et al. *Managing chemotherapy-related cardiotoxicity in survivors of childhood cancers*. *Paediatr Drugs* 2014; 16(5): 373-89). However, none of them can be used for personalized risk assessment before the initiation of chemotherapy.

The present invention provides a novel predictive model based on the combination of ten selected circulating miRNAs that can be used to stratify cancer patients at risk of cardiotoxicity.

The definition of this microRNA signature for cardiotoxic risk in cancer patients can be used for decision making of treatment regimens together with the monitorization of cardiotoxicity in cancer patients treated with anthracyclines.

Brief description of the drawings

Figure 1. Venn diagram of the overlap of miRNA profiles differentially expressed between cases and controls in miRNAseq array and list of the 10 miRNAs.

Figure 2 (A, B). Graphics showing relative values of the 10 miRNAs (miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p) in controls and cases (N=100) as detected by qPCR. Results are expressed as mean±SEM. A.U. stands for arbitrary units. * $P<0.05$.

Figure 3. (A) Determination of probability of developing cardiotoxicity (positive result) using a beta mixed model assessing the association between left ventricular ejection fraction (LVEF) and the miRNA included in MirCaTox. **(B)** Area under the ROC curve (AUC) showing sensitivity and specificity of the model.

Figure 4. (A, B) Graphics showing modulation of miRNAs by Doxorubicin in human cardiomyocytes and patients' serum. Left panels show copy number of indicated miRNAs in cardiomyocytes in culture before or after the addition of Doxorubicin (1 μ M) for 24 h. Right panels show copy numbers of indicated miRNAs as detected by RNAseq in serum from control patients and cases and expressed as mean $\pm$ SEM (N=10 in each case) before or after completion of anthracycline chemotherapy. Only miRNAs showing a similar tendency in cells and patients' serum are illustrated. * P <0.05.

Figure 5 (I-J). Target genes of the 10 miRNAs (miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p).

Figure 6. Cardioprotective effects induced by overexpression of miR-30b-5p, miR-150-5p and miR-4732-3p in neonatal rat cardiomyocyte cultures (NRCMs) treated with Doxorubicin (1 μ M) for 24h in terms of cell viability (CCK8 assay) and percentage of apoptotic cells (Anexin-V positive cells). Results are expressed as mean $\pm$ SEM. Cell viability is normalized to viability showed in cultures transduced with a negative control (NC) miRNA mimic and non-treated with Doxorubicin. * P <0.05, ** P <0.01

Figure 7. Reoxygenation after ischemia modulates expression of MIRCATOX miRNAs. Effect of ischemia followed by reperfusion (I/R) in miRNA-4732-3p and miRNA-150-5p levels as quantified by qPCR. Absolute copy numbers of miRNAs are indicated in cardiomyocyte cultures treated or not with I/R culture conditions. Results are expressed as mean $\pm$ SEM. * P <0.05.

Figure 8. Cardioprotective effects induced by overexpression of miR-150-5p and miR-4732-3p in neonatal rat cardiomyocyte cultures (NRCMs) subjected to 7h ischemia (defined as deprivation of oxygen and nutrients) followed by 30 min reperfusion (reoxygenation and nutrient supplementation) in terms of decrease of reactive oxygen species (ROS) and apoptosis (Anexin V) in NRCMs. Results are expressed as mean $\pm$ SEM. A.U. stands for arbitrary units. * P <0.05.

Detailed description of the invention

The present invention provides with new biomarkers of prediction of cardiotoxicity risk in cancer patients receiving, or susceptible to receive, anthracyclines chemotherapy.

5 In particular, the authors have developed a microRNA signature consisting of 10 circulating miRNAs: miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, that allows the identification of patients with high risk to suffer a decline of cardiac function after anthracyclines treatment.

10 The alteration of the expression of these miRNAs, comparing with the expression of said miRNAs in a control subject, not suffering from cardiotoxicity, is indicative of cardiotoxicity risk.

15 In the present invention, a control subject is a cancer patient not suffering from cardiotoxicity after anthracycline treatment.

For the purposes of the present invention, cardiotoxicity is defined, according to the most recent clinical guidelines, as the presence, in transthoracic echocardiography performed by a qualified physician, of one of the following situations:

- 20
1. A reduction of Left Ventricle Ejection Fraction (LVEF) $>5\%$ to a final LVEF $<55\%$, with symptoms of heart failure, or
 2. A reduction of LVEF $>10\%$ to a final LVEF <55 , without the presence of symptoms.

25 According to the above, in a main aspect, the present invention refers to the use of a set of 10 circulating miRNAs, consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, as biomarker of prediction of
30 cardiotoxicity risk in cancer patients receiving, or susceptible to receive, anthracyclines chemotherapy.

This new miRNA signature has allowed the authors of the invention to develop a method for predicting cardiotoxicity risk in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy. This method comprises the following steps:

- 5 i. Determining the expression levels of a combination of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, in a biological sample isolated from the patient, and
- 10 ii. Comparing the expression levels determined in i) with the expression levels of said miRNAs from a biological sample isolated from a control subject,

15 wherein the alteration of the expression of these miRNAs, comparing with the expression of said miRNAs in a control subject not suffering from cardiotoxicity, is indicative of cardiotoxicity risk.

20 In addition, based on this miRNA signature, the authors of the present invention have developed methods that, linked to an algorithm, allow cardiotoxicity to be detected with a probabilistic value, which is very useful in making clinical decisions. These methods can be used to screen cardiotoxic risk in patient's cohort receiving anthracyclines treatment or that are going to be subjected to anthracyclines chemotherapy and be used as powerful tools for cardiotoxic risk stratification of cancer patients.

25 Preferably, the probability of suffering from cardiotoxicity in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy is calculated according to the following formula:

$$\Pr(Cardiotoxicity) = \frac{e^{LP}}{1 + e^{LP}}$$

30 wherein,

$$LP = -1.228 - 0.041*miR4732 - 0.066*miR22 - 0.02*miR30b + 0.081*miR16 - 0.053*miR148a + 0.012*miR192 - 0.009*miR150p - 0.055*miR215 + 0.0899*miR486$$

5 Therefore, in another aspect, the present invention refers to an in vitro method for predicting the cardiotoxicity risk probability in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy comprising:

- 10 a) Determining the expression levels of a combination of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, in a biological sample isolated from the patient, and
- 15 b) Introducing the expression data obtained in a) in the following equation:

$$Pr(Cardiotoxicity) = \frac{e^{LP}}{1 + e^{LP}}$$

wherein,

20
$$LP = -1.228 - 0.041*miR4732 - 0.066*miR22 - 0.02*miR30b + 0.081*miR16 - 0.053*miR148a + 0.012*miR192 - 0.009*miR150p - 0.055*miR215 + 0.0899*miR486$$

The obtained result (Pr(cardiotoxicity)) is the expected probability of cardiotoxicity.

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The miR92b-3p is used intrinsically in the equation, since it was the miRNA that was used to normalize the values of the rest of miRNAs obtained by qPCR. This miRNA is appropriate for the normalization, according to qPCR method specifications for miRNAs amplification.

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The combination of the 10 miRNAs is valid to predict cardiotoxicity risk both before or once the chemotherapy has been initiated.

For the purposes of the invention, the determination of the miRNAs expression levels could be carried out by different techniques of Molecular Biology, for example qPCR or any other alternative technique generally used in the state of the art.

5 In a preferred embodiment, the biological sample isolated from the sample is a liquid biopsy (serum, plasma, urine, blood, etc). In a more preferred embodiment, the liquid biopsy is serum.

10 In a particular embodiment, the patient receiving, or susceptible to receive, anthracyclines chemotherapy is a breast cancer patient.

The modulation of the expression of the miRNAs included in the miRNA signature of the present invention result in a cardioprotection effect of cardiomyocyte cells. Accordingly, in another main aspect, the present invention refers to a method for the prevention of cardiotoxicity, in patients receiving or susceptible to receive anthracyclines chemotherapy, that comprises modulating the expression levels of the set of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p.

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Examples

Materials and Methods

25 The study was carried out according to the principles of the Declaration of Helsinki. The researchers assured that the privacy of the patients is guaranteed. All procedures were approved by local and national ethical committees. Written informed consent was obtained from each patient.

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Study design

Prospective observational study

Study population

Breast cancer patients post- or pre-antineoplastic treatment, > 18 years old at time of inclusion.

5 *Main study parameters/endpoints*

The primary endpoint is the development of cardiotoxicity, defined as the most recent clinical guidelines: The presence, in transthoracic echocardiography performed by a qualified physician of one of the following situations:

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1. A reduction of Left Ventricle Ejection Fraction (LVEF) >5% to a final LVEF <55%, with symptoms of heart failure.

or

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2. A reduction of LVEF >10% to a final LVEF <55, without the presence of symptoms.

Patients

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The study population included 137 patients with different types of breast cancer that were going to receive anthracyclines. The number of positive cases of acute cardiotoxicity was 10.2%. The period for inclusion of patients was 3 years. The follow-up duration was 2 years.

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The study population consisted of HER2-negative and HER2-positive breast cancer patients (n=137). These patients were scheduled to undergo three different adjuvant therapies as indicated:

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1) TAC chemotherapy consisted in Docetaxel 75 mg/m², Doxorubicin (Adriamycin) 50 mg/m² and Cyclophosphamide 500 mg/m², cycled every 21 day for 6 cycles (N=22).

2) AC chemotherapy consisted in Doxorubicin (adriamycin) 60 mg/m² and Cyclophosphamide 600 mg/m² cycled every 21 days for 4 cycles and then

Paclitaxel (80 mg/m²) or Docetaxel (100 mg/m²) weekly for 12 weeks or cycled every 21 days for 4 cycles respectively (N=90).

3) CAELIX chemotherapy, the same treatment that AC chemotherapy but with Liposomal doxorubicin (Caelix) instead Doxorubicin (adriamycin) (N=15).

4) FEC (N=4)

5) Taxanes (N=7)

Clinical data collection

Clinical data was collected before and after receiving antineoplastic treatment. Data include demographics, medical history, cardiovascular risk factors, use of concomitant medication and/or antineoplastic regimens, symptoms and signs of cardiovascular disease, results of physical examination, echocardiography and routine laboratory results.

Serum sample collection

Blood samples were taken before chemotherapy directly before infusion and after completion of treatment in non-heparinized tubes. After two hours clotting, serum was harvested and stored at the Biobank of Hospital La Fe.

RNA extraction

miRNA isolation was performed used miRNeasy kit (Qiagen Inc) according to the manufacture's instruction. Serum samples were thawed on ice and centrifuged for 10 min at 10,000g 4°C. The supernatant of serum was added to QIAzol lysis reagent containing MS2 RNA and a known number of copies of cel-miR-39 as internal control. After vortex the mix, chloroform was added, and samples were incubated at room temperature for 5 min. Tubes were centrifuged for 15min at 12,000g at 4°C. 420 µl from the aqueous phase obtained after centrifugation was mixed with 280 µl of 100%

ethanol. This mixture was loaded into an RNeasy minElute spin column in a 2mL collection tube and followed by centrifugation. The column was sequentially washed with Buffer RWT (700µl) and Buffer RPE (500 µl) twice. The miRNA was eluted with 35 µl of RNase-free water.

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Reverse transcription

Reverse transcription (RT) was performed using miRCURY LNA™ Universal RT microRNA PCR Kit (Exiqon) following manufacturer's instructions. Briefly, 2µl of RNA was mixed with 5x Reaction Buffer (2µl), Enzyme mix (1µl) and nuclease free water (5µl) to a final volume of 10µl. The mix was incubated for 60 min at 42°C followed by transcriptase heat-inactivation by incubating 5 min at 95°C. The product was frozen down until used.

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miRNA quantification

The quantification was performed using miRCURY LNA™ Universal RT microRNA PCR Kit and following manufacturer's instructions. Briefly, the cDNA was diluted in a 1/80 proportion in nuclease free water. 4 µl of diluted sample was mixed with 5µl of PCR Master Mix and 1 µl of PCR primer set to a final volume of 10 µl each well. The temperature cycle program used for amplification was: 95°C for 10 min, followed by 40 cycles at 95°C for 15 s and 60°C for 1min. Real-time quantitative PCR was performed using the ViiA™ 7 Real-time PCR System (Applied Biosystems, Carlsbad, USA). Real-time monitoring of the PCR reactions was performed with the QuantStudio Real-Time PCR Software and DataAssist v3.01 (Applied Biosystems). Standard curves were made in parallel using a synthetic sequence of each miRNA. Hsa-mir-92b expression level was used as house-keeping control.

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NRCMs isolation

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Neonatal rat cardiomyocytes (NRCMs) were isolated from newborn rats of 0-2 days old. Briefly, the newborn rats were euthanized by decapitation, their bodies were rinsed in ethanol 70% and the hearts were extracted in a laminar flow cabin. Hearts were minced in chunks of 1 mm³ and then incubated with trypsin at 4°C in agitation

O/N. Next day the tissue fragments were incubated with a solution of collagenase II/DNase at 37°C 30' and then were filtered through a 40 µm cell strainer to collect the cells. Cells were preplated for 2 h to purify the cardiomyocytes and then plated at a density of 150000 cells/cm². The NRCMs were maintained in Dulbecco's Modified Eagle Medium (DMEM) High Glucose (Gibco-Invitrogen®) supplemented with 10% fetal bovine serum (FBS, Gibco-Invitrogen®), ciprofloxacin (MERCK), sodium pyruvate (MERCK) and L-glutamine (Gibco-Invitrogen®).

Cell transfection and DOX treatment

NRCMs were transfected using Lipofectamine® 3000 (ThermoFisher) according with manufacturer's protocol. We prepared Lipofectamine® 3000 and the Mimic separately in OptiMem (ThermoFisher), then mixed and incubated 15' at room temperature. Finally, we added the transfection complexes to the NRCMs and incubated for 24 h. We treated the NRCMs with doxorubicin for 24 h with Doxorubicin 1 µM after cell transfection.

Ischemia-reperfusion injury model in vitro

An oxygen and glucose deprivation (OGD) protocol was established in our laboratory to mimic I/R-induced injury *in vitro*. NRVMs were incubated in none glucose DMEM (Gibco®) supplied with 1% of antibiotic mixture containing P/St (Sigma-Aldrich®) and submitted to a 1% O₂ and 5% CO₂ environment in a humidified incubator at 37 °C for 7 h (Ischemia, I). Reperfusion (R) was induced by subsequent incubation of cells with full high glucose DMEM medium (Gibco®) in 21% O₂ and 5% CO₂ atmosphere at 37 °C for 1 h. Cells cultured in normoxia (Nx) with full high glucose DMEM medium were used as control.

Cell viability assay

In order to evaluate the viability of the NRCMs after the treatments, we used the Cell Counting Kit 8 (CCK8, MERCK) assay following the manufacturer's instructions. The optical density of the cultures was measured at 450 nm in each well 4 h after incubation with the CCK8 assay solution.

Annexin-V staining

To determine the percentage of apoptotic cells in the NRCMs, we performed an Annexin-V staining using the FITC Annexin V Apoptosis Detection Kit (BD Pharmingen). After the treatments the NRCMs were stained with Annexin-V and then analyze by flow cytometry.

Reactive oxygen species (ROS) measurement

Oxidative stress was measured using CellROX® Orange Reagent (C10443, Molecular Probes). Briefly, NRVMs were submitted to I/R protocol as described before and incubated with CellROX® Orange Reagent solution and Hoescht33342 (1:2000, Thermo Scientific®). Live cells were visualised by In Cell Analyzer 2200 (GE Healthcare, UK) and orange intensity per cell was quantified with IN CELL Developer Tool software.

Echocardiography

Echocardiography was performed before and after the complete chemotherapeutic regime, and at 12 and 24 months after the end of the treatment. Conventional echocardiography consisted of two dimensional, and Doppler blood flow measurements to assess left ventricle (LV) structure and global function. All measurements were taken in accordance with the current guidelines of the American Society of Echocardiography using the iE33 (Philips Medical Systems, Andover, MA, USA) with transthoracic S5-1 and X5-1 broadband transducers (frequency= 1–5 MHz). Digital echocardiographic data were acquired during passively held end-expiration for offline analysis using a dedicated software. Parasternal long axis view was used to measure septal and posterior wall thickness and LV systolic and diastolic diameters. Cross-sectional images were recorded from the apex, and end-diastolic and end-systolic areas and LV lengths were measured from the apical four-chamber (A4C) and two-chamber (A2C) views (using the modified biplane Simpson's method) for the calculation of ejection fraction. The mitral flow velocity was measured by pulsed wave Doppler obtained in A4C view, with the sample volume positioned at the tips of the mitral valve leaflets. Peak early diastolic velocity - E wave, peak late diastolic velocity – A wave and E/A were calculated. All tracings were made by a single

observer at a centralized reading center who was blinded to all other clinical or biomarker data.

Interactome analysis

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Functional blocks from Go biological process are used in this analysis. The tables below show the count of functional classes enriched in each of the comparisons and using each of the two databases. A significance level of 0.05 was used (ie. functional blocks are called enriched if their corrected p-value is smaller than 0.05). Enriched functional blocks are classified into:

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- up-regulated in the first biological condition compared to the second one
- down-regulated in the first biological condition compared to the second one, and
- not enriched.

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The case of the GO database is special in that the functions or blocks of genes are organized into a directed acyclic graph (DAG) structure (https://en.wikipedia.org/wiki/Directed_acyclic_graph). This makes many of the significantly enriched functions to be redundant among them. In the second table of results of the functional profiling using the GO database we display just the significant and non redundant terms (functions); That is, the more specific terms among the significant ones.

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Statistical analysis

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Since the analysis of RNAseq data can be very sensitive to the modelling decisions taken at each step, three different methods were employed to search for differentially expressed genes between positive and negative patients: Robinson and Smyth exact negative binomial test, Random Forest test and Elastic net test. The results of this analyses produced the list of miRNAs able to predict risk to suffer cardiac dysfunction after completion of chemotherapy. To develop a predictive algorithm for cardiotoxicity risk, a logistic mixed effects model considering the different previously selected miRNA as potential fixed effects predictors and the individuals as a random factor was adjusted. Variable selection was performed using Akaike's Information Criterion

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(AIC), selecting the model with the lowest AIC. Performance of the final model was assessed by estimating the Area under the ROC curve (AUC) and also a bootstrapped optimism-corrected version of it. P values < 0.05 were considered statistically significant.

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All statistical analyses were performed using R (version 3.3.1) and R-packages randomForest (version 4.6-12), glmnet (version 2.0-10), NBPSeg (version 0.3.0), lme4 (version 1.1-12) and rms (version 4.5-0).

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Results

Cardiac function in terms of left ventricular ejection fraction (LVEF) in a cohort of 137 breast cancer patients receiving anthracycline chemotherapy were analyzed. Demographic data is shown in Table 1. From this cohort, 37 were discarded by incomplete data or sample collection.

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Table 1. Clinical characteristics of the study population

Demographics	Controls	Cases
Age (years)	54.75±12.42 (35-76)	53.46±15.71 (37-69)
Sex (% female)	85 (100)	15 (100)
BMI	26.43±5.16	26.09±5.41
Medical History		
Hipertension (%)	16 (18.8%)	1(6.6%)
Diabetes mellitus (%)	6(7.0%)	2(13.3%)
Dislipemy (%)	31(36.4%)	3(20.0%)
Smoking (%)	13(15.3%)	2(20%)
Histological subtype of cancer		
Triple Negative	14(16.5%)	4(26.5%)
Luminal A	5(5.9%)	1(6.6%)
Luminal B	9(10.6%)	2(13.3)
HER2/Neu	5(5.9%)	3(20%)
Medication and cumulative		

dose		
Taxanes	615±285	-
TAC	491.34±13.19	465.33±70.81
AC	390.52±9.81	366.40±20.61

From the final cohort (n=100), hematological parameters and serum biomarkers were determined before (Pre), after the last cycle of chemotherapy (Post) and one year after completion of chemotherapy (Rev), and the results are shown in Tables 2 and 3.

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Table 2. Hematologic parameters

			Pre	Post	Rev
White blood cells	Leucocytes (10 ³ /μl)	Control	6.64±2.14	5.39±0.19	5.48±0.68
		Cases	6.36±1.81	5.62±1.04	5.53±0.77
	Neutrophils (10 ³ /μl)	Control	3.85±1.87	1.40±0.06*	3.2±0.8
		Cases	3.80±1.60	1.29±0.17*	3.29±0.9
	Lymphocytes (10 ³ /μl)	Control	2.09±0.70	3.29±0.18	1.93±0.55
		Cases	1.88±0.71	3.41±0.93*	1.57±0.48
Red blood cells	Erythrocytes (10 ³ /μl)	Control	4.49±0.47	4.16±0.05	4.29±0.14
		Cases	4.20±0.50	4.12±0.15	4.45±0.40

Table 3. Serum biomarkers

			Pre	Post	Rev
Cholesterol	Control		216.68±3.81	223.23±4.50	205.7±51.90
	Cases		219.17±13.43	214.80±28.01	201.5±52.69
Triglicerides	Control		104.16±5.30	148.77±13.96*	117.09±18.82
	Cases		78.17±3.42	100±21.33	93.00±22.60
Glucose	Control		103.86±3.50	97.32±2.20	113.45±10.73
	Cases		101.51±2.64	121.33±16.18	95.33±4.70
Creatinin	Control		0.67±0.01	0.64±0.01	
	Cases		0.64±0.03	0.56±0.02	
usTnT	Control		4.27±0.0.32	14.39±0.98**	
	Cases		4.47±0.38	11.17±1.80**	

Cardiac function was monitored in these patients at these three timepoints (Pre, Pst, Rev) and, in some patients, a decline in LVEF and left ventricular end-diastolic diameter (LVEDD) to pathological levels, as defined for cardiotoxicity in the clinical guidelines, was observed (table 4).

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Table 4. Cardiac function parameters

Cardiac function parameters		Pre	Post	Rev
LVEF (%)	Control	65.86±6.15	63.30±7.75	63.38±5.94
	Cases	63.31±7.87	56.56±12.38*	48.20±8.81***
LVEDD (%)	Control	43.28±0.51	42.67±0.50	43.99±0.58
	Cases	42.44±2.39	46.62±2.00	43.60±2.25

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter

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Among them, 10 patients that suffered cardiotoxicity during treatment defined as a decrease in 10% of FEVI below 55% (cases) were selected, and 10 additional matched patients with no affection of cardiac function (controls). Next miRNAseq analysis using Illumina platform were performed and 200 miRNAs were detected and normalized by relative abundance.

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Using three regression models, Random Forest, Negative Binomial and Elastic Net, the most differentially expressed miRNAs (n=10) between cases and controls were selected.

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The random forest model achieved a cross-validated accuracy of 100% (100% sensitivity and 100% sensibility). It selected 18 miRs as the most important predictors for discriminating both groups. The Robinson and Smyth exact negative binomial test found significant differences between both groups in four miRs, three of them also present in the 18 miRs selected by random forest. Elastic net selected 16 miRs. Two of them were included in the 18 selected by the random forest model and, of those, one was also included in the 4 selected by the Robinson and Smyth test. A Venn diagram is provided to visualize the combined results of the three modeling approaches (Figure 1). One miR has been selected by the three methods (hsa-miR-4732-3p), two have been selected by random forest and the exact negative binomial test (hsa-miR-150-5p and hsa-miR-215-5p/192-5p) and another has been selected

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by elastic net and random forest (hsa-miR-92b-3p). The rest of the selected miRs are the following: only selected by Robinson and Smyth exact negative binomial test: hsa-miR-148a-3p; only selected by Random Forest: hsa-miR-16-5p, hsa-miR-22-3p, 25-3p, hsa-miR-26a-5p, hsa-miR-423-5p, hsa-miR-451a, hsa-miR-486-3p/486-5p, hsa-miR-92b-3p, among others; only selected by Elastic Net: hsa-miR-30b-5p/30c-5p, among others.

Next, the expression of the 10 most significant miRNAs out of 23 miRNAs was validated (called the MirCaTox signature), in the final cohort by qPCR including the patients used in the RNAseq study. Relative values of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p were normalized to the expression of miRNA 92b-3p as described in Materials and Methods section (Figure 2). The demographic data and clinical characteristics of the final cohort resembled the previously selected cases and controls for the RNAseq study. As expected, there was a correlation between the RNAseq and qPCR. Both techniques detected a differential expression in miRNAs defined in MirCaTox between cases and control.

Verified levels of these miRNAs were used to build a predictive model of cardiotoxic risk using a logistic mixed effects regression model. An example of algorithm using this set of miRNAs for predicting cardiotoxic risk is represented below by the following equation:

$$\Pr(\text{Cardiotoxicity}) = \frac{e^{LP}}{1 + e^{LP}}$$

Where

$$LP = -1.228 - 0.041*miR4732 - 0.066*miR22 - 0.02*miR30b + 0.081*miR16 - 0.053*miR148a + 0.012*miR192 - 0.009*miR150p - 0.055*miR215 + 0.0899*miR486$$

This model achieved an area under the curve ROC (AUC) of 0.81 (Figure 3). This model was integrated in a software that could aid to get a probabilistic value of cardiotoxic susceptibility after input MirCaTox values for a given patient.

To investigate the biological significance of this miRNA cocktail, target genes of miRNAs included in MirCaTox were identified (figure 5). Among them, cardiac specific genes like TNNT2 and ACTG1 were found. These genes belong to the sarcomeric machinery of cardiac muscle cells. Accordingly, it is likely that desregulation in miRNAs included in MirCaTox signature will affect the long term function of cardiac cells.

Next, an interactome of MirCaTox, that combined direct and secondary interactions of miRNAs and proteins, was performed to identify regulated biological processes by this miRNA cocktail. Most representative pathways are shown in Table 5.

Table 5. Regulated biological processes in comparison of controls and cases in serum samples taken before chemotherapy. ID indicates the code number of gene ontology (GO)

ID	Lor	Pval	Name
GO:0040018	0,83	0	positive regulation of multicellular organism growth
GO:0010171	0,995	0	body morphogenesis
GO:2000052	1.108	0,001	positive regulation of non-canonical Wnt signaling pathway
GO:0043536	1.036	0,001	positive regulation of blood vessel endothelial cell migration
GO:0090042	1.191	0,002	tubulin deacetylation
GO:0051123	0,747	0,002	RNA polymerase II transcriptional preinitiation complex assembly
GO:0072202	1.235	0,003	cell differentiation involved in metanephros development
GO:0070897	0,679	0,003	DNA-templated transcriptional preinitiation complex assembly
GO:0061005	0,754	0,003	cell differentiation involved in kidney development
GO:0060271	0,301	0,003	cilium morphogenesis

GO:0014902	0,468	0,003	myotube differentiation
GO:0010165	0,673	0,003	response to X-ray
GO:0006261	0,356	0,004	DNA-dependent DNA replication
GO:0035116	0,971	0,004	embryonic hindlimb morphogenesis
GO:0006790	0,367	0,004	sulfur compound metabolic process
GO:0033262	1.064	0,004	regulation of nuclear cell cycle DNA replication
GO:0030195	0,883	0,004	negative regulation of blood coagulation
GO:0050819	0,883	0,004	negative regulation of coagulation
GO:1900047	0,883	0,004	negative regulation of hemostasis
GO:0072089	0,388	0,004	stem cell proliferation
GO:0060325	0,876	0,004	face morphogenesis
GO:0060242	1.122	0,005	contact inhibition
GO:0001656	0,549	0,005	metanephros development
GO:0006266	0,814	0,005	DNA ligation
GO:0072659	0,298	0,005	protein localization to plasma membrane
GO:0048854	0,752	0,005	brain morphogenesis
GO:0006893	0,601	0,005	Golgi to plasma membrane transport
GO:0019985	0,571	0,005	translesion synthesis
GO:0043001	0,733	0,006	Golgi to plasma membrane protein transport
GO:0032535	0,256	0,006	regulation of cellular component size
GO:0033260	0,802	0,006	nuclear cell cycle DNA replication
GO:0046112	0,848	0,006	nucleobase biosynthetic process
GO:0044272	0,474	0,007	sulfur compound biosynthetic process

GO:0090002	0,32	0,009	establishment of protein localization to plasma membrane
GO:0035137	0,808	0,009	hindlimb morphogenesis
GO:0060020	0,984	0,009	Bergmann glial cell differentiation
GO:0051188	0,432	0,009	cofactor biosynthetic process
GO:0050818	0,484	0,009	regulation of coagulation
GO:0021697	0,796	0,01	cerebellar cortex formation
GO:0051291	-0,335	0,01	protein heterooligomerization
GO:0045815	-0,353	0,01	positive regulation of gene expression, epigenetic
GO:0006323	-0,254	0,009	DNA packaging
GO:0002244	-0,328	0,009	hematopoietic progenitor cell differentiation
GO:0043201	-1.041	0,009	response to leucine
GO:0050728	-0,491	0,008	negative regulation of inflammatory response
GO:2000756	-0,482	0,008	regulation of peptidyl-lysine acetylation
GO:0032438	-0,984	0,008	melanosome organization
GO:0009749	-0,351	0,008	response to glucose
GO:0072576	-0,888	0,008	liver morphogenesis
GO:0071103	-0,217	0,007	DNA conformation change
GO:0019083	-0,241	0,007	viral transcription
GO:0006342	-0,324	0,007	chromatin silencing
GO:0006336	-0,491	0,007	DNA replication-independent nucleosome assembly
GO:0055075	-1.073	0,007	potassium ion homeostasis
GO:0019080	-0,235	0,007	viral gene expression
GO:0031050	-0,625	0,007	dsRNA fragmentation
GO:0070918	-0,625	0,007	production of small RNA involved in gene silencing by RNA
GO:0040016	-1.025	0,007	embryonic cleavage
GO:0009746	-0,353	0,007	response to hexose

GO:0034724	-0,487	0,007	DNA replication-independent nucleosome organization
GO:0002440	-0,38	0,007	production of molecular mediator of immune response
GO:0000338	-0,892	0,006	protein deneddylation
GO:1903307	-1.008	0,006	positive regulation of regulated secretory pathway
GO:0006414	-0,279	0,006	translational elongation
GO:0001974	-0,723	0,006	blood vessel remodeling
GO:0002700	-0,481	0,006	regulation of production of molecular mediator of immune response
GO:0006406	-0,353	0,006	mRNA export from nucleus
GO:0065005	-1.067	0,005	protein-lipid complex assembly
GO:0006497	-0,549	0,005	protein lipidation
GO:0002697	-0,271	0,005	regulation of immune effector process
GO:0019058	-0,181	0,005	viral life cycle
GO:0044033	-0,234	0,005	multi-organism metabolic process
GO:0000183	-0,619	0,005	chromatin silencing at rDNA
GO:0050434	-0,539	0,005	positive regulation of viral transcription
GO:0043486	-0,524	0,004	histone Exchange
GO:0002706	-0,468	0,004	regulation of lymphocyte mediated immunity
GO:0048385	-1.084	0,004	regulation of retinoic acid receptor signaling pathway
GO:0035196	-0,686	0,004	production of miRNAs involved in gene silencing by miRNA
GO:0045637	-0,319	0,004	regulation of myeloid cell differentiation
GO:0043902	-0,37	0,004	positive regulation of multi-organism process

GO:1901533	-0,902	0,003	negative regulation of hematopoietic progenitor cell differentiation
GO:0042158	-0,546	0,003	lipoprotein biosynthetic process
GO:0045653	-1.357	0,003	negative regulation of megakaryocyte differentiation
GO:0048771	-0,43	0,003	tissue remodeling
GO:0016311	-0,234	0,003	Dephosphorylation
GO:0071604	-1.018	0,003	transforming growth factor beta production
GO:0071634	-1.018	0,003	regulation of transforming growth factor beta production
GO:0042541	-1.057	0,003	hemoglobin biosynthetic process
GO:0020027	-0,984	0,003	hemoglobin metabolic process
GO:0002703	-0,415	0,003	regulation of leukocyte mediated immunity
GO:0071705	-0,205	0,003	nitrogen compound transport
GO:0031055	-0,601	0,003	chromatin remodeling at centromere
GO:0051028	-0,333	0,003	mRNA transport
GO:0006417	-0,247	0,003	regulation of translation
GO:0034284	-0,381	0,002	response to monosaccharide
GO:0009743	-0,36	0,002	response to carbohydrate
GO:0016233	-0,707	0,002	telomere capping
GO:0048524	-0,407	0,002	positive regulation of viral process
GO:1901532	-0,637	0,002	regulation of hematopoietic progenitor cell differentiation
GO:0034080	-0,667	0,002	CENP-A containing nucleosome assembly
GO:0061641	-0,667	0,002	CENP-A containing chromatin organization
GO:0045638	-0,524	0,002	negative regulation of myeloid cell differentiation

GO:0051168	-0,322	0,001	nuclear export
GO:0031348	-0,493	0,001	negative regulation of defense response
GO:0045652	-0,974	0,001	regulation of megakaryocyte differentiation
GO:0044346	-1.095	0,001	fibroblast apoptotic process
GO:0050657	-0,343	0,001	nucleic acid transport
GO:0050658	-0,343	0,001	RNA transport
GO:0051236	-0,343	0,001	establishment of RNA localization
GO:0032906	-1.146	0,001	transforming growth factor beta2 production
GO:0032909	-1.146	0,001	regulation of transforming growth factor beta2 production
GO:0046784	-1.185	0,001	viral mRNA export from host cell nucleus
GO:0051290	-0,903	0,001	protein heterotetramerization
GO:0015931	-0,345	0,001	nucleobase-containing compound transport
GO:0006403	-0,343	0	RNA localization
GO:0030219	-0,716	0	megakaryocyte differentiation
GO:0006405	-0,425	0	RNA export from nucleus
GO:0006413	-0,302	0	translational initiation
GO:0006987	-1.285	0	activation of signaling protein activity involved in unfolded protein response
GO:0006335	-1.156	0	DNA replication-dependent nucleosome assembly
GO:0034723	-1.156	0	DNA replication-dependent nucleosome organization
GO:0010804	-1.127	0	negative regulation of tumor necrosis factor-mediated signaling pathway

GO:0006446	-0,587	0	regulation of translational initiation
GO:2000269	-1.351	0	regulation of fibroblast apoptotic process
GO:0016458	-0,349	0	gene silencing
GO:0031047	-0,526	0	gene silencing by RNA

Significant biological processes are listed by P value (pval). Lor positive value is indicative of increased levels of miRNAs with the consequent repression of biological processes whereas Lor negative value is indicative of decreased levels of miRNA what would result in desrepression of target genes in cases versus controls. Thus, a repression of Wnt signaling pathway, a known pathway involved in heart development, together with repression of biological processes related to blood vessel development, endothelial cell migration, embryonic hind limb morphogenesis, myotube differentiation and sulphur compound metabolic process, were observed, what are also related to cardioprotection. The ERK1/2 signalling pathway is involved in sulphur dioxide preconditioning-induced protection against cardiac dysfunction in isolated perfused rat heart subjected to myocardial ischemia/reperfusion (*Huang P et al. Int J Mol Sci. (2013); Hydrogen sulphide attenuates cardiac dysfunction in a rat model of heart failure: a mechanism through cardiac mitochondrial protection. Wang X et al. Biosci Rep. (2011); "Hydrogen sulfide attenuates cardiac dysfunction in a rat model of heart failure: a mechanism through cardiac mitochondrial protection. Wang X, et al. Biosci Rep. 2011 Apr; 31(2):87-98; Garcia NA1, Moncayo-Arandi J1,2, Vazquez A1, Genovés P1, Calvo CJ3, Millet J3, Martí N4,5, Aguado C4,5, Knecht E4,5, Valiente-Alandi I6, Montero JA1, Díez-Juan A7,8, Sepúlveda P. hydrogen sulfide improves cardiomyocyte function in a cardiac arrest model. Ann Transplant. (2017) May 9; 22:285-295*). Moreover, this miRNA combination was related to increase in coagulation and hemostasis. In contrast, biological processes like translational initiation, nuclear export, RNA localization, response to carbohydrate, tissue remodelling, transforming growth factor beta production and regulation of tumor necrosis factor-mediated signalling pathway and fibroblast apoptosis were unrepressed.

Assays in cardiomyocytes

The specific signature of miRNAs has been detected in serum. Since the pathways related to miRNAs are linked to cardiomyocytes, the copy number of the miRNAs of interest in human cardiomyocytes was also measured. As observed in **Figure 4**, the miRNAs previously detected in serum were also present in human cardiomyocytes (left panels) and their expression level is altered when cells are damaged by Doxorubicin. Moreover, the effect of Doxorubicin on cardiac cells resulted in similar modulation than the variation observed in patients. As shown in the right panel of figure 4, the copy number of miRNA-22-3p increases both in cells and serum of patients after anthracycline treatment whereas miRNA-30b, miRNA-148a, miRNA-150-5p, and miRNA-4732-3p decrease their expression levels. These results enforce the usefulness of the signature of miRNAs presented in this patent as sensor of cardiac wellness. Indeed, this set of miRNAs regulates genes involved in the aforementioned biological pathways (Figure 5)

Finally, we wanted to see if modulation of miRNA levels could result in cardioprotection of cardiomyocyte cells in culture. For this purpose, we transfected NRCMs with miRNA mimics and evaluated their cardioprotective effect in terms of increase in cell viability and decrease in apoptosis in comparison to non-treated cultures after doxorubicin treatment (Figure 6). As observed, miR-30b-5p, miR-150-5p and miR-4732-3p protected NRVCN against doxorubicin treatment. To test if cardioprotection could be extended to other types of injury we set up an *in vitro* experiment where cells were submitted to ischemia followed by reperfusion (I/R) as explained in materials and methods. Since reoxygenation induce both cell survival and apoptosis, we observed a strong upregulation of miR-150-5p and miR-4732 (**Figure 7**), indicating that therapies aiming to modulate MirCaTox miRNAs could result in therapeutic targets to prevent cardiotoxicity. Moreover, when we performed overexpression of miR-150-5p or miR-4732-3p in NRVCN and subjected them to I/R, transfected cells showed reduced levels of ROS and apoptosis (Figure 8).

CLAIMS

1. Use of a set of 10 circulating miRNAs, consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p,
5 as biomarker of prediction of cardiotoxicity risk in cancer patients susceptible to receive anthracyclines chemotherapy.
2. A method for predicting cardiotoxicity risk in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy comprising:
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 - i. Determining the expression levels of a combination of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, in a
15 biological sample isolated from the patient, and
 - ii. Comparing the expression levels determined in i) with the expression levels of said miRNAs from a biological sample isolated from a control subject not suffering from cardiotoxicity,
- 20 wherein the alteration of the expression of these miRNAs, comparing with the expression of said miRNAs in a control subject, is indicative of cardiotoxicity risk.
- 25 3. A method for predicting the cardiotoxicity risk probability in a cancer patient receiving, or susceptible to receive, anthracyclines chemotherapy comprising:
 - a. Determining the expression levels of a combination of 10 circulating
30 miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p, in a biological sample isolated from the patient, and
 - b. Introducing the expression data obtained in a), in the following formula:

$$\Pr(\text{Cardiotoxicity}) = \frac{e^{LP}}{1 + e^{LP}}$$

wherein,

$$LP = -1.228 - 0.041 \cdot \text{miR4732} - 0.066 \cdot \text{miR22} - 0.02 \cdot \text{miR30b} + \\ 0.081 \cdot \text{miR16} - 0.053 \cdot \text{miR148a} + 0.012 \cdot \text{miR192} - 0.009 \cdot \text{miR150p} - \\ 0.055 \cdot \text{miR215} + 0.0899 \cdot \text{miR486}$$

and wherein the obtained result is the expected probability of cardiotoxicity (Pr(cardiotoxicity)).

4. Method according to claim 1, wherein the biological sample is a liquid biopsy.
5. Method according to claim 4, wherein the liquid biopsy is serum.
6. Method according to claim 1, wherein the patient is a breast cancer patient.
7. A method for the prevention of cardiotoxicity in patients receiving or susceptible to receive anthracyclines chemotherapy that comprises modulating the expression levels of the set of 10 circulating miRNAs consisting of miRNA 16-5p, miRNA 22-3p, miRNA 30b-5p/30c-5p, miRNA 92b-3p, miRNA 148a-3p, miRNA-150-5p, miRNA-192-5p, miRNA 215-5p, miRNA 486-3p/486-5p and miRNA-4732-3p.

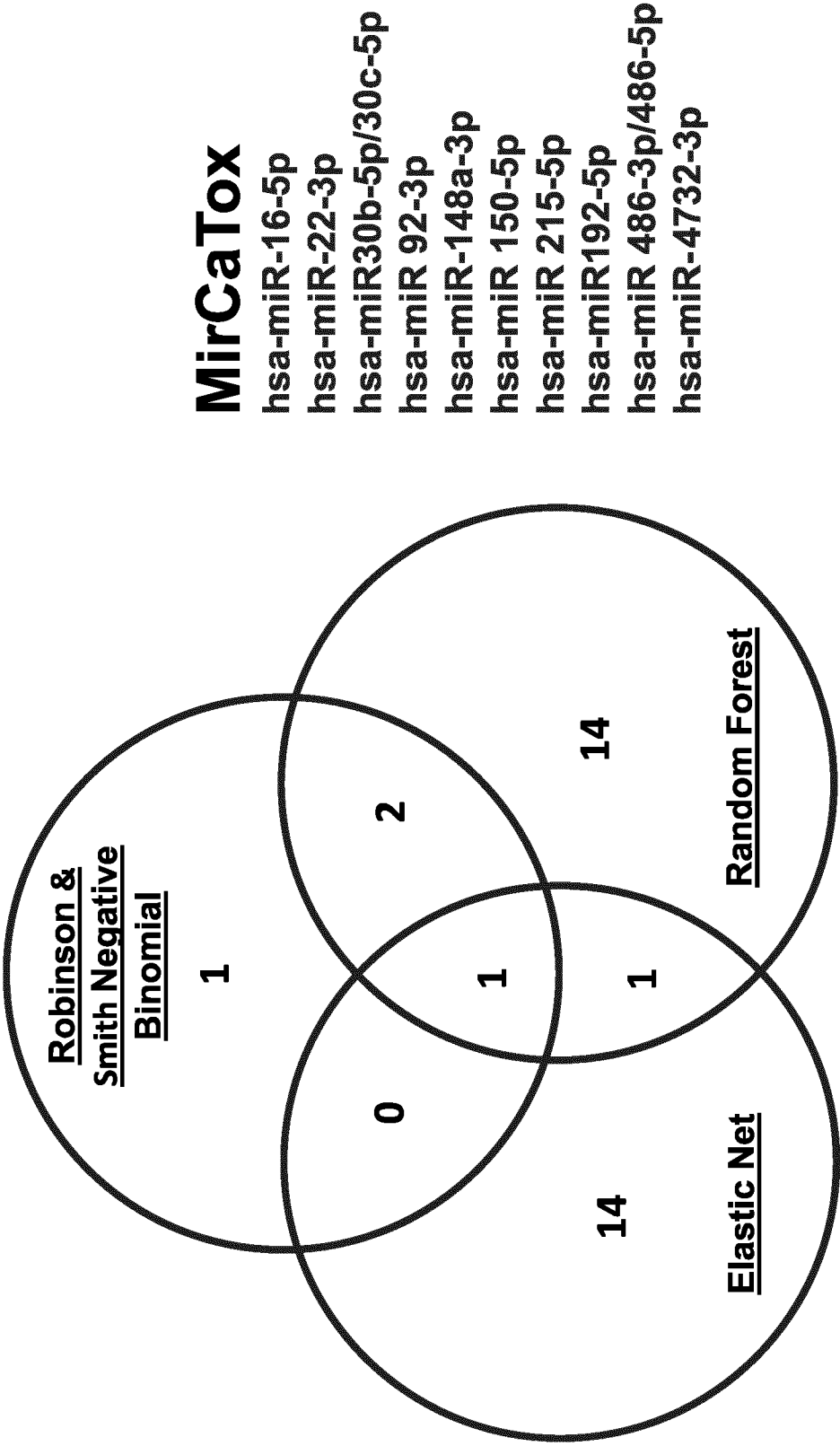


FIG. 1

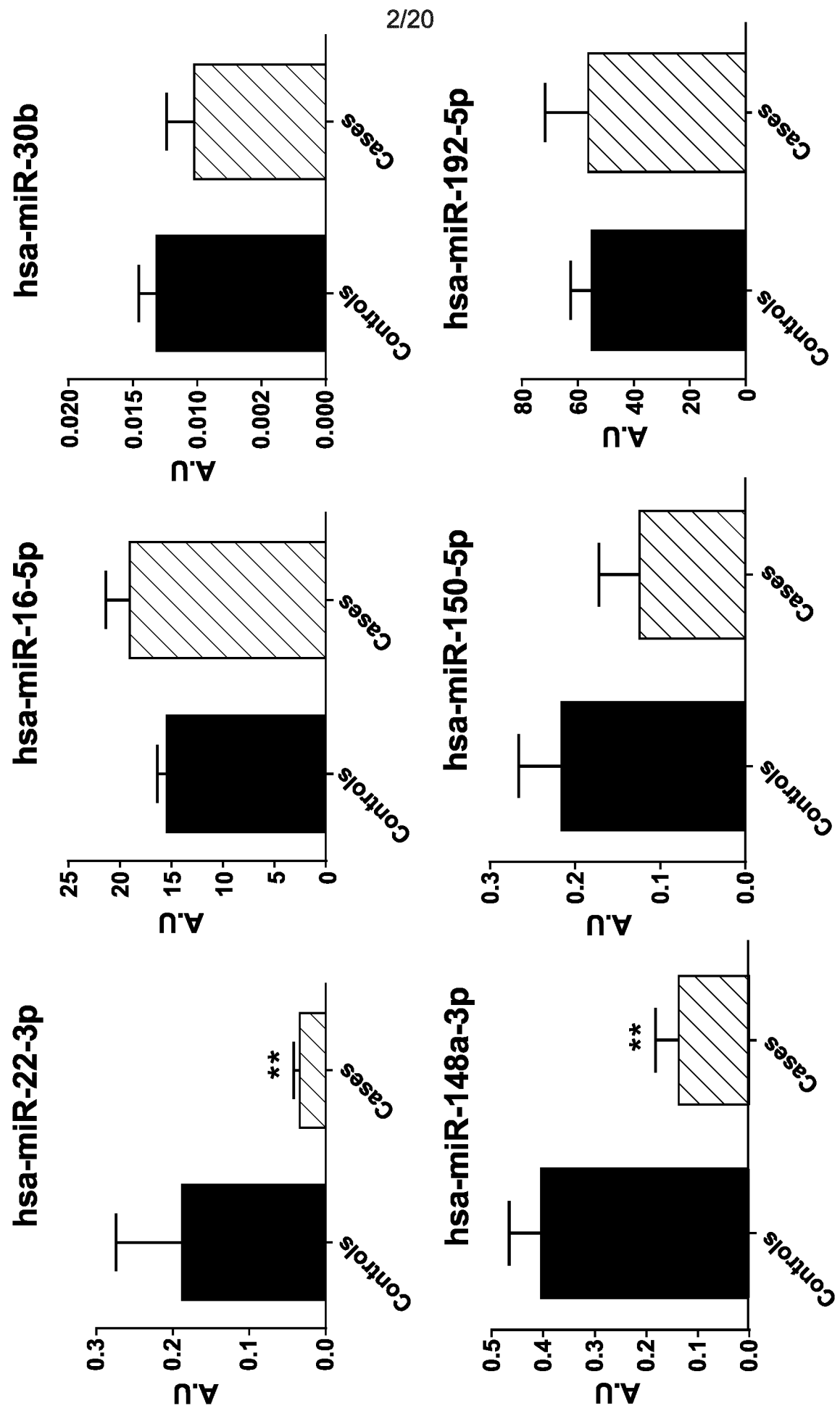


FIG. 2A

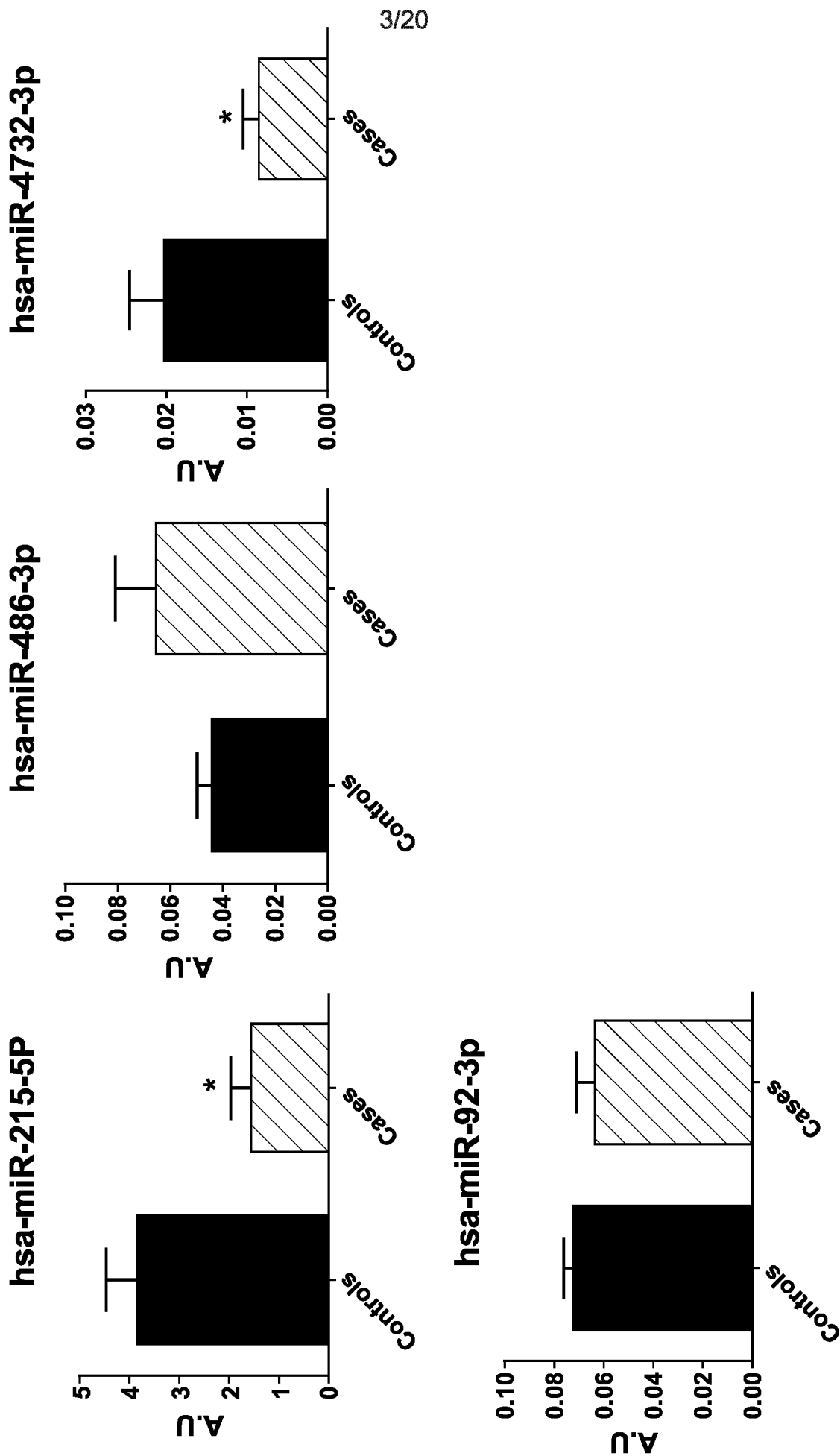


FIG. 2B

$$\text{Pr(Positive)} = \frac{e^{-1.228 - 0.041 \cdot \text{miR4732} - 0.066 \cdot \text{miR22} - 0.02 \cdot \text{miR30b} + 0.081 \cdot \text{miR16}_{5p} - 0.053 \cdot \text{miR148a} + 0.012 \cdot \text{miR192} - 0.009 \cdot \text{miR150p} - 0.055 \cdot \text{miR215} + 0.0899 \cdot \text{miR486}}}{1 + e^{-1.228 - 0.041 \cdot \text{miR4732} - 0.066 \cdot \text{miR22} - 0.02 \cdot \text{miR30b} + 0.081 \cdot \text{miR16}_{5p} - 0.053 \cdot \text{miR148a} + 0.012 \cdot \text{miR192} - 0.009 \cdot \text{miR150p} - 0.055 \cdot \text{miR215} + 0.0899 \cdot \text{miR486}}}$$

FIG. 3A

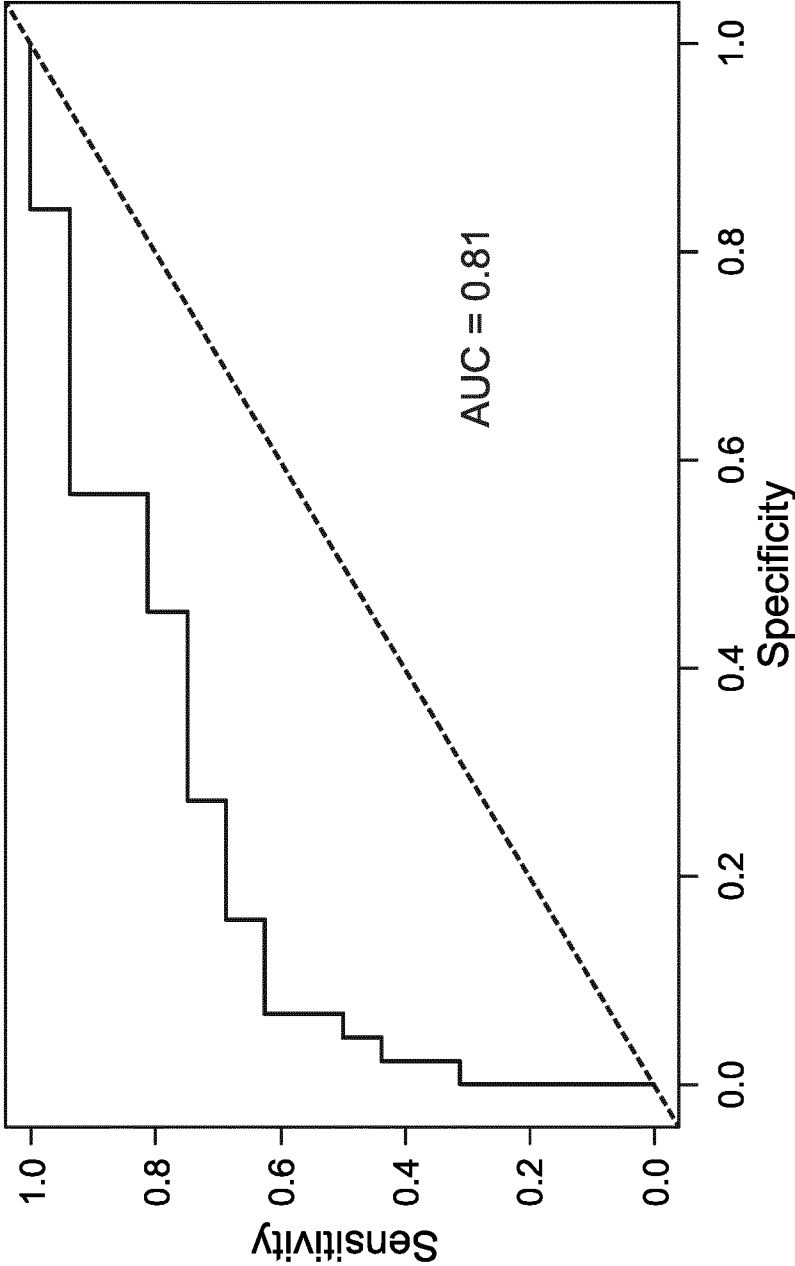


FIG. 3B

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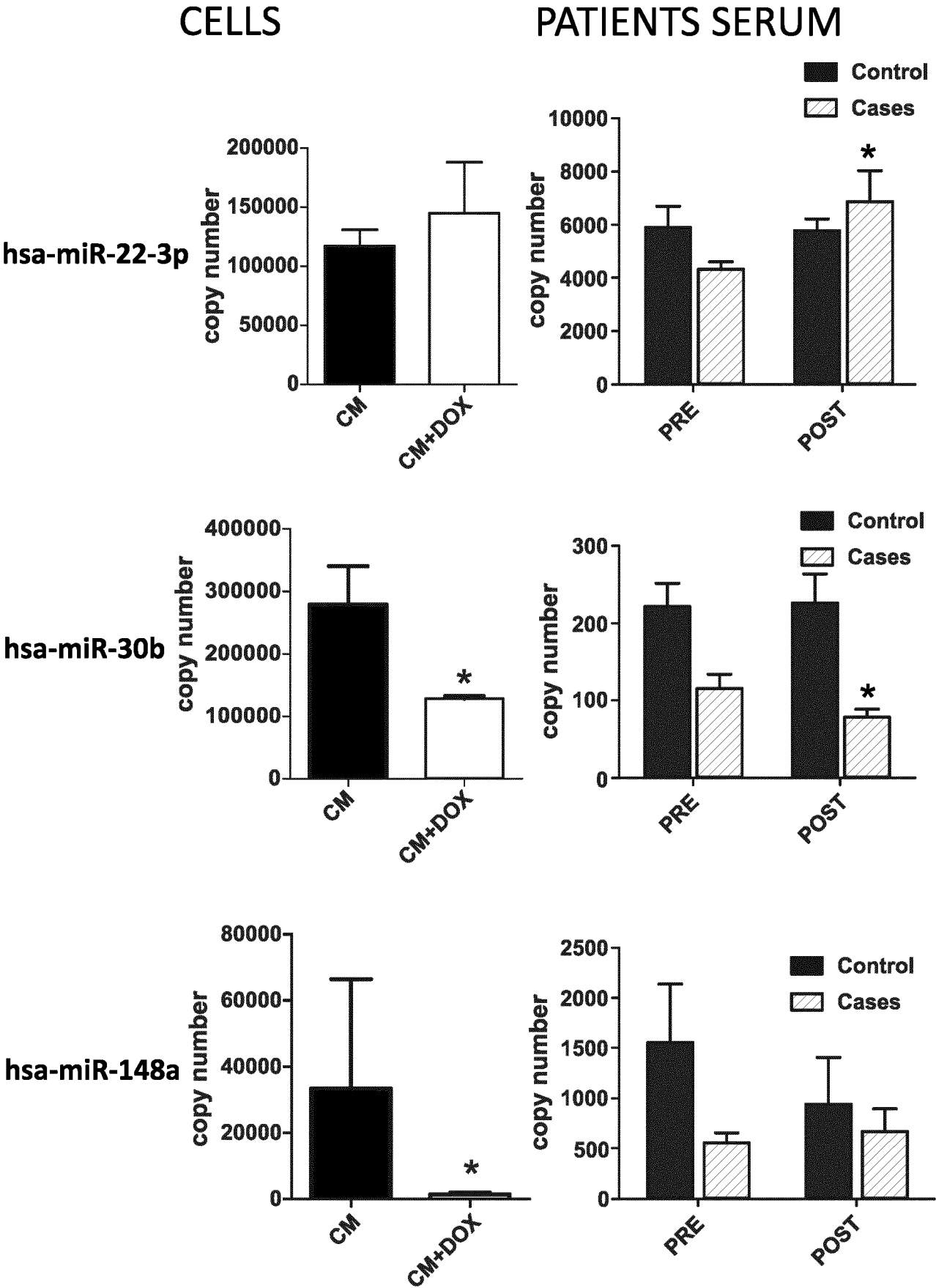
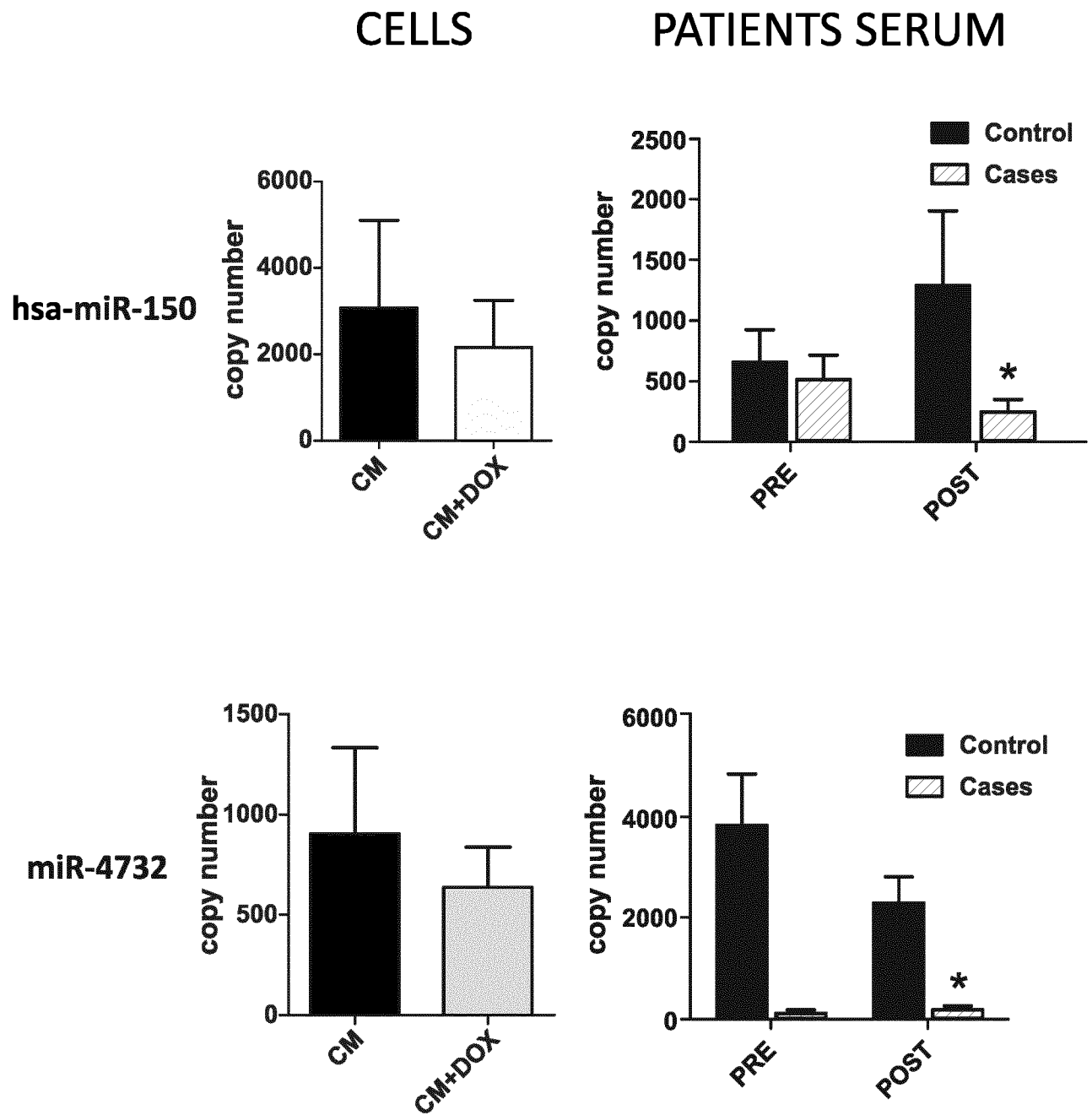


FIG. 4A

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**FIG. 4B**

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
HSNPA	TRMT112	JUN	CCNE1	HSPA6	ERRF1	Ncoa2	DNAH14	CPM	SYNPO
HIST1H4A	KLHL25	SF1	HSPA4	LHX1	ZCCHC10	SMARCC2	NADK	HSPA4	CPM
HSPA4	HECTD1	PIH1D1	GCOM1	CAMK1	RNF10	SMARCC1	HIST1H4A	MOCS1	BUB1B
HSPA8	ZRANB1	POLR3C	SRSF12	ANXA2P2	NCBP1	ACTG1	FTSJ2	MFAP3	SSFA2
P4HA1	ERBB2IP	POLR3A	DYNLL1	PPHLN1	CRKL	RB1	TRIM14	SQLE	SEC23IP
MFAP3	HSPA5	PFDN6	ATPIF1	WDR5	HSPA9	NELFB	ZRANB3	DLG1	UBAC1
LEMD3	NRCAM	SMIM21	DLG1	CTNNAL1	HSPA8	ZNF70	UBE2QL1	C11orf30	DBN1
DLG1	GLRX3	ANAPC16	DLG3	C2CD5	HIPK3	FBXO11	PLK1	RMND5A	HAUS1
ZNF703	IKBKB	DIAPH2	DLG2	WIPI2	B2M	BUD31	HIGD1A	ALOXE3	LGALS1
FAM114A1	AKT1	CREB5	DLG4	NUP93	MFAP4	PPARGC1A	NDUF85	BCAT1	SMG5
ZMYM6	RBM4B	KRTAP3-2	RPF2	STK3	SRSF10	RPS4X	BBX	MTUS2	SMG7
NUP98	PKP4	AIF1L	LOC101060521	ZNF175	MFAP1	E2F1	TRMT61A	TNNT2	DLG2
MUC1	NOSTRIN	MTUS2	TAZ	ERJ3	SRSF12	JPH1	FTSJ3	MON2	DLG4
ELOVL1	IKBKG	ATP2B2	NOB1	CEP70	DBN1	AFF1	SETD1A	KCNJ6	OARD1
PRR14	KIFAP3	CSNK2A1	ESPL1	CTBP1	AGT	PPWD1	LRFN1	AKAP3	ZNF703
ZNF775	UBAC1	URI1	SV2C	TNKS	ATP6V1B2	ZNF24	NGDN	MBTD1	TPM4
HSD17B12	TMEM177	KRTAP10-9	CBLC	ATP6V1A	MBV12A	ZNF71	ZNF512	CEP70	TNNT2
CAPZB	AL645728.1	KRTAP10-8	ARHGEF11	LMO4	HSPA5	TARSL2	SRSF12	ATMIN	ALMS1
FBXW11	NDUFAB1	CD3EAP	CAMK2D	NOP2	LARP1	LOC1	S100A13	ZSCAN12	GRWD1
RPS27L	SNRNP200	KRTAP10-5	MUC1	POLR1D	PIK3CA	LRPPRC	RASAL2	TNFSF13	PRIM1
ATP2A3	DLG3	KRTAP10-3	SP7	STIP1	PIK3CB	RARA	DEPDC1B	TNFSF12	OFD1
TNNT2	DKK3	KRTAP10-1	IQCG	TNNT2	NAPG	FTSJ3	USP21	ACTA1	METT17
SFXN3	NFE2L2	KRTAP10-7	CSF3R	APOB	CRBN	ZNF384	MOAP1	EVL	WDR1
SFXN1	SMARCB1	APP	LRP6	WDR47	ZC3H14	ZNF354A	GNL2	ANO4	ARHGEF17
SWAP70	MAP3K7	HIRIP3	RSU1	WDR48	OLIG1	HIST1H1A	EP300	UBE2D2	SRFBP1
XPO1	PPP2R4	RPL8	GATA3	LNK1	VAC14	BHLHE40	ZNF354A	ITGA7	SRP14
XPO7	NAV1	RPL9	POLR3F	EFTUD2	DHX8	BHLHE41	RBPJ	IMPAD1	IL2RB
GTF2B	GOLGA2	KAT2B	UBE4A	ZIC2	CBLB	THRB	CPT2	GABBR1	CAMK2B
MAPK1IP1L	DLGAP1	POLR1A	POLR3G	HOXB9	ATP8	DCC	DDX31	CHKA	CEP89
PDLIM1	UBR5	POLR1B	CCND1	HOXB6	ZMYM6	ZFP2	CBFA2T2	UFSP2	FXR2
HIST2H3C	CDK9	POLR1C	TPI1	HIST2H3A	DIAPH1	CRNKL1	PCF11	XPO4	ABLIM1
GART	MALT1	POLR1D	ACLY	ARL5B	WDR1	HSP90AB1	ANKMY1	MRFAP1L1	CEP83
ING1	NUP214	POLR1E	YBX1	ATAD5	MUC1	GOLGA2	FAM110B	EPPK1	MUC13
ANAPC7	MAPRE1	NCKAP5L	YBX3	TOP1	PPP2R2A	DKC1	ZC3HAV1	DMAP1	GTF2F1
RPS6KA5	SETDB1	RUVBL1	UBE2D2	APITD1	AGER	CDH1	P3H1	KSR1	AKAP2
ZC3H3	MAPRE2	XPO7	UBE2D3	KRT17	PIK3C2B	sep-14	DYRK1A	GTF2I	ZNF174
PSMD10	ENTPD6	RUVBL2	UBE2D1	FLNB	GC	CDH3	C3orf17	TSPYL4	WHSC1
IL15RA	HMGAI	BACH1	POLR1A	FLNC	CSF3R	KDM2B	DYRK1B	CCDC57	GTSE1
KLHL22	MRPL35	KRTAP4-2	POLR1B	EIF4A1	COX6A1	sep-11	ZFP62	AKTIP	DDX47
SMAD6	TAP1	KRTAP9-4	POLR1C	ANKRA2	FAM172A	sep-10	ZMYM2	ING3	GADD45GIP1
GOLPH3L	NUP98	CCT4	POLR1D	EIF4A3	WDTC1	SF3A1	ZMYND8	ATAD1	PRR14
VAPB	MF12	KBTBD8	XPO1	EIF4A2	MAX	ZMYM2	TBC1D25	ITGAV	LAT
VAPA	KRT23	ZBTB34	TANK	SMS	SRSF8	CENPN	FNTB	KIAA1377	ZNF281
DCTN2	MUC1	SIRT7	ZNF454	VAPA	ARHGAP12	DDIT3	CAMK2D	GOSR1	ACTA2
DCTN1	TRIM27	EFEMP2	SOX10	SMAD3	CSN2	CENPK	PRRC2B	INA	CAPZB
NCOA1	TRIM21	KRTAP10-11	MRPL17	DCTN2	LAT	POTEI	PRRC2A	SDCCAG8	ACTA1
ACAT1	COG5	POLR2E	EFTUD2	DCTN3	PAIP2B	CENPI	CAMK2G	SLC2A14	RRP1B
DDB1	COG4	ASTN2	ISG15	PLP2	CCDC114	TPM3	CLCN7	VAPB	MYO18A
LONRF2	USP39	POLR2F	WSB1	DCTN1	TSG101	TRIM24	CAMK2A	VAPA	DYNC1I2
CTNNB1	CGNL1	POLR2L	TBC1D25	GPRC5A	FKBP2	SP1	TRIM22	LINC00852	HIP1R
CAPZA1	NUPL1	POLR2H	VTA1	RL2	RPS27A	MGP	IWS1	EVPL	ARNTL
WASL	NUPL2	ANAPC7	EEF2K	FAM74A4	MYO18A	TRIM27	PJA1	TRIM55	CCT8
RCVRN	HBB	SUPT6H	FUNDCl	SMC3	POLR1D	PRMT6	FXR2	DCTN6	BMS1
BAD	CSNK2A1	CDC27	ZNF227	ACTR10	RNPS1	RPL17	ANKRD34A	TNFSF13B	APOB
ERH	ARID5B	CDC26	SEN3	RAD51AP1	XPO1	BRD8	MUC19	NEDD8	MRPL16
HIST2H4A	FDP5	RBPMS	GARS	S100A9	CCT8	RFC3	CCDC155	RBM12	CCT2
UBTF	DNAJA1	SHISA6	ZNF878	RBM14	WDR44	RPL13	BRD4	BEND7	CCT3
IMPDI1	PTGES3	PDRG1	POLR2E	S100A6	XPO7	BRD4	GPATCH4	Ube2g2	SOX13
ACAA2	KIF5B	MYBBP1A	KCNH1	TNKS1BP1	CCT2	COPS3	GIGYF1	LRIG3	CCT7
POTEI	AKT2	MYH15	CAMSAP3	UBE2V2	CCT3	CENPU	AARS2	NOL6	UACA
ILVBL	DDX47	SPRY2	PPP1R2	SCAF8	PIKFYVE	EIF2B1	TESK2	ABT1	CCT5
TIMM50	TRA2A	SPRY1	CBL	CMBL	CCT7	ZAK	KCTD13	A2ML1	JAK3
GFAP	MICAL3	NOTCH2NL	RASAL2	GOLGA8EP	CCT4	ZNF445	SYNCRIP	CRTAP	JAK1
KPNB1	IPP	MGAT5B	FRAT1	NAA30	CCT5	ZYG11B	VAT1	IPO11	ZNF512
KRT40	CHTF8	POLR2K	FRAT2	LEO1	EPPK1	NVL	YWHAZ	MORC4	CCDC50
MCFD2	TMEM14B	GPN1	ZNF350	RBM6	JAK2	MYL12A	TAIF2	ACTR10	TBC1D2B
ENDOD1	APC	RANBP3	ATXN3	PSMD9	JAK1	KRTAP10-8	PPP2CA	ZNF496	XPOT
ANKFY1	UQCRCF51	KRTAP5-6	EIF4A3	LAPTM4B	BRCC3	SIN3B	WHSC1	PLCG1	TPRN

FIG. 5A

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
BTRC	APP	PFDN2	ABHD17B	SGMS2	TMEM128	APP	APP	GPATCH2L	DST
Mpp6	IL24	RIMBP3	MAP3K1	WDR82	EPS15L1	MAZ	CAMK2B	H3F3A	QRFR
FAS	TNKS	CARS	GIGYF1	WDR1	PPARA	RBBP7	ZNF845	PPFIA1	DSP
RPN1	RASGRP3	JUND	TLE1	IFT81	WDR77	EIF2A	NINL	SKA1	ANAPC5
RPN2	POM121C	TAF1C	VAPB	DYNC111	RPRD2	RBBP4	POP1	DYM	CIZ1
SF1	REL	TAF1B	SMAD3	NUDC	C21orf58	NR1I3	PLEKHA7	ZMYND19	ATAD5
IKKB	DIRAS3	ZNRD1	XIAP	RAI1	FTL	ARHGAP17	CEP70	ITGB1	DZANK1
RASAL1	RPL9	HIRA	ANKRD32	YLP1M1	TNK2	DDX6	LIMA1	HEATR1	WDR34
MARCH9	MED21	WDR92	AKAP11	FIP1L1	PREPL	CEP70	SURF6	KPNB1	WDR36
EGF	PNISR	RPL10A	DCTN3	CNOT7	SMYD5	RNF8	LZTR1	KRT40	WDFY3
CTSS	SNX9	MYO9A	TSC2	CNOT6	SH3D19	NR1I2	CP51	IL37	FLOT1
CDCA3	MACF1	CSNK2B	TSC1	KYNU	PSMD14	GRIP1	GLYR1	THAP1	PDE6D
RAN	KHDRBS1	SSRP1	BRIX1	HIST4H4	PSMD11	EIF5A2	ZNF771	EIF4E2	MYBBP1A
ANKRD13A	FAM98A	EEF1A1	CIITA	FGFR1OP	CBL	TAF5L	SIRT3	HAP1	RRP12
PLEKHH3	HOXC6	EEF1A2	PLRG1	TYMSOS	APOH	SARS	DTL	HMBBOX1	FLNA
GMCL1	SPECC1L	TFF1	SAP30BP	EIF4E3	KRT17	CTCF	RRP8	ARSK	FLNB
FADD	ST14	TNNT2	RBM14	TBL1X	KRT16	ATXN2L	SPTAN1	ZNF398	FLNC
RELA	WIF1	RPAP3	NAT9	TBC1D23	KRT15	TNKS	RPL4	MAP3K15	MYH10
UQCRRF51P1	SFXN2	KIAA1522	BEND3	ACTR1A	KRT14	BATF	FUBP3	WDR73	MPP7
TPR	KIF23	SMARCA5	H2-Aa	EWSR1	WDFY3	MESDC2	DCLK1	SERPINA12	SHROOM3
SNAI1	BAZ2A	NOP58	RXRA	SPRED1	GIT1	VDR	ZCCHC9	TGM5	KIAA0586
RNF19A	NCKAP5	UBTF	PRKAR1A	SF1	SERBP1	SNX7	PUM2	NAP1L5	XIAP
ZC3H11A	RXC2	CCT6B	LMO4	PRPF8	POLR2A	CTNND1	SFXN3	IKKB	PSMD9
APP	AP2B1	SUPT16H	GEMIN4	PKP1	KRT19	SNX5	IFNGR2	MARCH6	TRIM56
SFN	STARD7	AC138655.1	CUL3	NUDT21	KRT18	ZNF184	TOMM22	RCBTB2	GPRC5A
UQCRRF51	NCKAP5L	KRT40	IFIH1	PRPF6	MYH11	COPS2	DHX30	GMCL1	NCOA1
MMAB	XPO1	RRN3	KRBA1	EIF3M	SNIP1	TRIM32	KAT7	MKLN1	NCOA6
UQCRC2	PPM1E	TRIP10	MDH1	DDX39A	PAG1	ACTA2	JADE3	HMG20A	TFPT
DDAH2	SRSF6	KRTAP4-12	EEF1A1	EIF3A	RET	RPL5	JADE2	PXYLP1	ELMSAN1
YTHDF3	TANK	ACTN3	CTNBN1	EIF3B	MKRN1	TRIM37	JADE1	PLBD1	RBM19
YTHDF1	SRSF3	ACTN1	Lzts2	EIF3C	AUNIP	SUDS3	KANSL3	ARRDC3	TCEA2
NEK4	ZNF454	ADAMTSL4	Zbed3	EIF3D	REL	RC3H1	TNNT2	APP	GRIPAP1
NEK1	TUBA1C	ACTN4	VPS25	EIF3E	DCTN2	EDC3	C21orf2	SLC2A3	PRKAR1B
DDX56	TCTN3	TSGA10	GB5	DYNLT3	RECQL5	MED1	RPL7A	YEATS4	NOL6
RRBP1	U2AF2	SIGLEC8	RAI1	ZNF264	DCTN1	sep-09	EBNA1BP2	ACTB	CAPZA2
C11orf54	SRSF9	TWISTNB	KLF5	MTMR4	TSC2	DENND4A	NEK1	NUP85	CAPZA1
DLD	ECH1	ATF7	KLF2	CENPO	CDC6	TNNT2	DDX52	SMARCE1	TRIOBP
DLAT	JUP	KRTAP9-2	DEFA1	CENPN	YTHDC1	DCP1A	SRGAP2	RUVBL1	MPRIP
NLRP3	C4A	ATF2	SIPA1L1	CENPM	TNNT2	RPL36AL	JUN	RUVBL2	TP73
CREBBP	CSTF1		EXTL3	HPCAL1	PLRG1	sep-05	ZBTB8A	ZBTB8A	LMO7
HDAC1	SNX33		IPO9	CENPK	SLC36A1	HHT1	TPRN	NCAPG	PINX1
ANKRD13D	KLHL8		KRT40	CENPI	ALAS2	ARID4B	PDPR	TUBB2A	CDC27
HSP90AA4P	CHEK1		FBN3	CENPH	S100A9	PNMA5	SAMD1	MRFAP1	RPS10P5
CLOCK	TCF4		IL33	CENPC	S100A8	ADRBK1	RBMX2	CEP170	CDK5RAP2
NLRP9	RAB16		PLEKHO1	LDB1	DDB1	SAP130	SURF1	CALML3	MYL6B
UBL4A	POM121		IGHM	TPR	STK32C	TIMM8B	FKBP1B	TRIM8	MORC3
MYO3B	RCN2		CPVL	CNOT2	RIF1	ARNTL	FNDC3B	HDAC1	CTTN
AKR1C4	PDLM2		PARD3	SH3BGR1	C17orf85	SDHAF1	PRPF6	TMEM131	KRBA1
AKR1C1	TOMM7		SLC35F1	CENPU	SS18	SAP30	TOP2B	STXBPA	ACTBL2
AKR1C2	MRPL18		BTRC	CENPT	PRKAR1A	IL7	HNMT	FANCD2	CDC23
AKR1C3	DST		MAP3K11	CENPQ	SH2B1	CHD9	GAR1	LINC00346	HMG81
SET	CHUK		KIF13B	CENPP	LTK	ZNF75A	TTC5	ZBTB10	PLCG1
NOTCH2NL	SENP1		EWSR1	ZC3H11A	SRPK2	FOS	MRPL11	SKP2	MAZ
SKP1	PRKAR1A		BZW2	ARID1B	ALK	JUN	DDX56	RACGAP1	EPS8
CDT1	ZNF24		ZFPM1	APP	LMO2	CAP1	TTC1	TPM2	AFAP1
WDR26	ACY1		LINS	IBA57	WASL	CAP2	TICAM1	WDR26	OIP5
WDR24	VHL		MARCH5	UQCRRF51	RADIL	JUP	EFEMP1	RANBP6	EPS15
MAPK1	CTBP1		PTK2B	YIPF2	CDC40	ZNF318	KIF18A	CST6	CDK19
RANBP3	SLC26A8		IKBK	TMEM43	CDC42	HTRA2	SEN5	SSX2IP	MAD1L1
CARS	ING5		USP28	YIPF6	CTTN	PIK3R1	EFEMP2	SAAL1	ATP13A2
SUMO1P1	PHLDB2		ARL2BP	CD2BP2	WDR6	NR1H4	CDK11B	TFIP11	CDCA2
SATB2	STRN3		PRPF4	SNX5	EGFR	BRMS1	COL4A5	SMEK1	ST5
EP300	EPAS1		USP21	ZNHIT2	RBPMS	MGEA5	HIST2H3C	RAD51	CLIP1
Mpp2	DAPK2		USP20	ZNF691	PLCG1	BAHCC1	ING4	SRCAP	SPTBN1
ERCC2	RBFOX2		NFE2L3	COP56	OSGEP	NR1H2	ING5	PHF12	RPGRIP1L
EZH2	TAF1		NFE2L2	DHX38	AHS6	NR1H3	PWP2	USP4	SIPA1L3
NR1D1	VAV1		NFE2L1	CCAR2	LARS2	RPL18A	CAPG	CEP57L1	SIPA1L2
NR1D2	ATP5C1		ARHGEF2	ADAR	CPSF3	TCF4	CBY1	IQGAP1	PSMC4
SMARCA4	CBL		STRAP	C11orf58	CAD	KPNB1	NUFIP1	ASAH1	PSMC5

FIG. 5B

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
UIMC1	WIZ		DOCK7	PKM	EPS15	DPYSL2	ZNF701	RB1	TTL6
YWHAZ	NUP153		CDH1	CNOT11	SIRPA	ACTB	TAF5	APOA1	CD44
UNC119	CSNK1E		RELB	IBTK	VPS28	STAT6	CCDC137	AMD1	KPNB1
ABCB7	KRT15		RELA	EIF4H	SRRT	KRT40	TP53	ZBTB9	VPS53
DNAJC11	KRT14		CENPB	AGMAT	AARSD1	VP552	RBFOX2	FAM207A	LCP2
C3orf38	EIF4EBP1		WDR47	EIF4E	IMPDH2	SAP30L	RPL15	TANC2	E2F7
INTS6	STRN		SNAI2	EIF4B	YLP1M1	UNC5D	PLSCR1	CYTH1	EXOC3
PNN	FLNA		SNAI1	MGA	ETNK1	IGFBP3	ELP3	CYTH3	EIF4E2
VCP	CD2AP		TESK2	CALML3	APCS	DPH2	FCF1	HBA2	TBL1X
HIST1H3E	LCK		RBM45	TTC19	PSMC2	POLR2A	MOK	PBX2	MYO6
HSPH1	KRT19		DBI	CALML5	HSD17B4	PPARA	BTD	PBX3	C9orf156
TOPBP1	AGFG1		Arhgef11	MEF2B	TRA2A	EIF4E	HIST1H3A	PBX1	KIF13B
UFD1L	MYH10		APP	MEF2A	TRA2B	PWP2	POLE3	CHST12	TNNI2
TIMM44	MYH11		CSAD	PROSC	C21orf91	NUFIP2	UTP23	MEAF6	WDR76
ACTG1	RASIP1		VIM	HDAC1	DDX17	TRIP4	RPL7L1	TYMP	UBTF
PODXL	TMEM126A		MRPL40	ACTA2	SPATA2L	ING2	MYBBP1A	TWISTNB	TRIM15
Magi1	GIGYF2		GAA	HDAC3	KPNB1	sina	RRP12	VTI1B	HUWE1
CWC22	BAG5		APC	MYH9	KRT40	UBE2I	HERC5	ZSCAN32	PES1
TOMM7	KIAA1467		UQCRCF51	HDAC4	HGS	EDA2R	TRIM3	ACTG1	DAB2
CERS2	NEB		XPENPEP1	HDAC9	LGALS3BP	ATG2B	ARHGEF26	TGM1	GNL2
DNMT1	ICOSLG		SPTAN1	FANCD2	LCP2	RELA	RPF2	RRP7A	Nme2
RORC	NDUFAF5		ATP5B	ZBTB10	SNW1	RPS6KA4	RBM28	RANBP10	PSMB10
NXPE3	EIF4E		COX6B1	NOTCH2NL	NCK1	NCOA4	MCM2	ZNF382	DYNLT1
MAGI1	ATP6VOA1		VANGL2	DNAJB1	CFH	RNASEH2C	HDAC1	GSDMA	GNG12
NUP214	AKAP13		DHX34	H1FX	OGT	PPARG	KDM1A	DNMT1	BRD2
CUL1	KRT5		DHX35	DNAJB5	TFG	AP1G2	HDAC2	MAP3K6	BRD3
CUL2	FRMD5		DHX36	DNAJB4	HEXB	Cap1	BAG6	MAP3K5	NOL10
CUL3	AMER1		DDX58	ETF1	NCL	POP1	HDAC4	ZNF479	CENPC
CCDC77	CTH		LCE1E	RANBP3	CREBBP	FAM195A	UBL4A	ZNF473	SSH2
PRMT3	ATP5E		KHSRP	PATL1	PNN	MCM4	BRD1	CUL1	CDC48
PRMT6	EOGT		SF3A1	KLHL11	SAE1	ZBTB24	SDCBP	LUC7L2	IL2RG
CREB1	STRN4		SF3A2	KRTAP5-6	PPP3CA	BATF2	SH3BP4	BRCA1	PXDC1
SLC25A20	HBA2		MGEA5	PODXL2	GUCA1B	BATF3	STOM	HLA-DPB1	ZNF280C
MIF	FBXO30		SH3BP4	SDIM1	SLC1A2	PCM1	XIAP	PRMT8	RP6-24A23.6
DNAJA3	SRSF7		Nono	DLL3	RBM45	TTC38	DAS2	BRCA2	RABGAP1L
ZAK	RACGAP1		UBE2E1	HAP1	GHR	ATXN2	UPF1	HAL	MRPL47
KPNA5	TELO2		UBE2E3	C11orf87	CBR1	MCM2	MTIF2	ANKS6	MRPL46
KPNA1	SMC3		LRFN1	KIF1B	NEFH	HDAC1	NVL	PRMT1	YEATS4
MYO5C	CCL5		SMYD2	PIP5K1C	DAB2	KDM1A	GMNN	LRRC1	DIXDC1
CARM1	NAV3		LARS	LENG1	PRPF3	HDAC3	VDAC2	BRD8	APC
HIF1A	BCL10		TRIM9	MCMBP	SLC25A13	HDAC2	VDAC1	FGFR2	ACTB
ARHGAP1	NAV2		TRIM8	LAGE3	CUL4B	HDAC4	MTG1	CTSV	MRPL48
PPM1G	RANBP9		VP551	RABGAP1	SIX5	CLOCK	DDX27	KAT8	PAK1
USP48	HNRNPM		WDYHV1	FAM188B	ARHGEF5	ACTA1	CDC6	BRK1	RPL37A
UBAP2L	MARK2		TRIM5	MGLL	MRFAP1L1	EIF1AX	CDIPT	MORN2	SPTAN1
KRTAP4-2	HNRNPAB		NIF3L1	SF3B3	RARS	EIF2B4	TNP02	RBBP7	MED1
SYT12	TRAPPC11		NUDCD3	NFYB	MIPEP	ZNF22	LRIF1	KAT5	MED6
UGP2	ZNF106		HDAC4	ITGB3BP	CCDC12	EIF2B2	EHMT2	TTC17	MED7
PIA2	ND4		RPLP1	SMARCA4	RELA	SDCCAG3	ALAS1	PRRX1	MED4
B4GALT5	RANBP2		PRKAR2A	RAD54B	NCKIPSD	SMAD2	ZNF624	ZBTB21	ARFGAP1
SULT1C3	RPS27		CFAP20	ATG16L1	ACIN1	EIF3E	NEDD1	DOCK7	MED8
POM121	ICOS		FASTKD5	PFKP	LPP	TBX2	CDT1	C4orf27	MED9
TUBB6	LAMA3		SNCAIP	HSPD1	CNOT1	RPS6	FAM53C	TNFRSF17	AP2B1
GBP7	LAMA4		PSEN1	NFKBIL1	SNRPD2	RPS10	PSMA3	FAM184A	NCKAP5L
GBP6	SLAH1		SNRPA1	C3orf38	SYNCRIP	MCRS1	R3HCC1	MEIS2	GTF2E1
PDP1	KIAA1328		ADAP1	YWHAE	FN1	ZBTB8A	SIPA1	MEIS1	BMF
CSE1L	FAM214A		TPBGL	CASC5	GFAP	AHNAK	PDCD6	JUP	SUB1
ASPCR1	IL7R		CST6	DDX23	APP	PLRG1	REEP3	RNF138	DDX50
PPP2R5C	PKP2		UFM1	DPH1	DOCK5	NPLOC4	DSG1	PGK2	FTSJ3
BAG6	TFF1		Prune	DPH2	VIM	IKZF1	KIF21A	GID4	CBX2
ASNA1	MTOR		LRSAM1	TRIM56	ECHS1	NCOR1	MORF4L2	EPN1	RAB11A
ILK	EXPH5		RRS1	CACNG1	UBA52	PNRC1	DID01	GID8	TAB1
KIAA0101	SND1		DOCK6	NDUF9B	CYLD	NCOA2	FBXW7	TRRAP	C6orf141
HARS	BBX		GAPDH	PODXL	TUBB4B	NCOA3	MVP	MB21D2	PLCH1
POFUT1	SAV1		AGAP1	PPII2	ACTB	NCOA1	NOP2	KPRP	PPP1R9B
SEC23A	SYNE1		SNW1	PPII4	SPTY2D1	NCOA6	MAGI1	SPICE1	PKN3
CAST	RAD51D		MTOR	POLR3C	STRADB	ZBTB16	MYEF2	PKNOX1	GCA
PSMA1	NT5DC2		JOSD1	SNRNP200	STAR10	STAT1	NSA2	PKNOX2	BUB1
VCPIP1	NT5DC3		KIF1C	DCD	FRS2	DDX31	ZNF668	PALB2	BUB3

FIG. 5C

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
DUS3L	FHOD1		YOD1	NUP214	FUS	GPR22	KIAA0020	CDC14A	C9orf43
PUS10	SRSF1		MFN2	TAGLN2	FUBP1	NR2F6	DDX21	MDFI	SHB
CTDSP2	SHCBP1		MFN1	ISL2	KHDRBS1	NEDD4	SYDE1	MSH6	UHRF1BP1L
PDHA1	NUP54		ISY1	PRPSAP1	AP2B1	SNRPA1	AGAP1	FBXO2	RNF214
ZC3HAV1L	RSRC1		XAB2	TRIM29	RUVBL1	MAPK3	SPATA24	C1orf43	PHLDB3
OCLN	ATP6V1E1		KIAA1191	USP39	ZBTB7B	GTF2A1L	UNG	RPS2	ZBTB20
NT5DC2	ACTL8		ACSBG1	MDM2	FLT3	MAPK1	RPS4X	CDSN	RNASEH2A
NT5DC3	SMU1		USP8	SETD5	VASP	FOSL1	USMG5	HSDL1	CALML3
AGXT	BCL7B		PTK2	RPL19	FIG4	PAK4	ALG13	STAT3	PPP5C
FARSB	FAM83B		UBE3A	SNRPD2	SF3A1	PSMA5	Act5C	MARK2	FCF1
SIGMAR1	SLC3A2		USP2	SNRPD1	PRR22	FASN	NAT10	FAM160B1	KDM3B
TTF2	NME2P1		SF3B1	CNN2	RSAD1	PATL1	NOP14	BRAF	VP551
MAP7	STX18		SF3B3	RNF185	RP11-169F17.1	BEND7	STAU1	ALOX12B	RALA
HIST2H2BE	RAPGEF2		USP7	PTPN11	Shc1	RPS24	ZFYVE21	MORF4L2	SSB
MID2	CSNK2B		SOX9	PTPN14	CSK	RPS27A	NMNAT1	MORF4L1	HDAC1
SPTBN1	RNF146		OTUB1	UTRN	TIFA	Bag6	BUD13	COL4A3BP	HDAC3
Lin7c	RPS17		SMARCA5	KPNA1	PLEKHS1	SIAH1	JPH2	CCDC33	HDAC2
RPL24	MCM3AP		OTUB2	LZTR1	CSR1P	SIAH2	KIF1C	CCDC30	CLOCK
TLN1	C2CD2L		CEBPB	SYNM	CCDC9	sep-08	PIP5K1A	NCCRP1	CIRBP
MBP	SPG7		AXIN2	C16orf70	BCAR1	HIST1H1T	DDX24	PRKAA1	TEX10
NET1	ERC1		AXIN1	AKNA	EPOR	KIAA0020	BOD1L1	BTAF1	RCOR1
PCNA	PSMD1		CYTB	GORASP1	SUPT6H	RXRA	WDR12	MAEA	ZNF195
SMARCB1	JUND		FYN	SMU1	RALY	APPL1	CXXC1	MAGEH1	C1QBP
MCM7	AGR3		DNAJC13	MAML1	PPP5C	UNC13D	RPS3A	KCNJ9	CBX8
ALPP	CTNNB1		CEBPZ	USP47	TUBB	gag	NSMCE2	ZNF408	INF2
SAMHD1	CYP17A1		PRKCI	JUP	NEIL1	DDX27	OGT	SBSN	MLF1
CRIP1	C17orf89		CDC5L	ALDH16A1	CLK2	EP300	ZBTB21	BIRC5	SKP2
ZNF865	CHD6		SBDS	SMEK1	CLK3	LSM14B	KIF21B	AIP	GAS2L3
PDK3	ANKRD17		NBR1	PARP1	SNX27	YTHDC1	STAU2	ECM1	SKP1
PDK2	CACYBP		WARS	RPP25L	BTB	CSNK1A1L	TOMM20	LOR	MECOM
EPM2AIP1	TAL1		GNB2	BCCIP	SNX25	FAM195B	KCTD3	MAP2K1	MYH9
MAPT	RPA2		SLA	GIN53	PDGFRB	KIF1A	MED4	HIST2H2BE	TPM3
SEC61A1	SPTBN2		CCNB1	UBE2K	TPM4	ARID5A	FAM110A	MID2	TPM2
RAE1	SPTBN1		DDX20	LMNB1	KRT73	NTN1	RPL32	DIO2	TPM1
PARG	ANKRD11		XPO6	TP53	TP53BP2	DHX30	RPS18	PDCD2L	KIAA1671
HECTD1	RPTOR		FIBP	GIN54	TCERG1	ATP6V1E1	ECM1	NEFM	SIPA1
SETD1A	KRT17		NOTCH2	HYOU1	SCYL3	ZFP62	TTF1	NAP1L1	RAB13
PUF60	LPHN1		NOTCH3	ATG12	SPRY2	WDR12	BAP1	NAP1L4	SKAP1
ATP2B3	TIMM17A		Dlgap2	MELK	ATR	PIAS1	MAP7	NEFH	AMBRA1
TROVE2	EEF1D		FKBP14	PHF7	STXB4	RPL10A	NOC4L	ZNHIT6	CEP250
ITSN1	AXIN1		PMAIP1	ADAMTS9	FABP1	ISY1	CPSF3	SUV39H1	MRPS18B
ANAPC16	MBD4		CRLF3	NDUFB11	ITIH4	HSP90AA1	MYOF	PIGQ	DOCK7
CIAPIN1	TFAP2A		Axin1	CD2	KIAA1549L	XAB2	CPSF1	KRTAP4-12	TRIM69
ZFP1	YWHAQ		UQCRCQ	KRT4	NOTCH2NL	TADA3	RERE	FAM9B	NUDT16
MYCBP2	FYN		GPR39	VDAC3	RACGAP1	DCP1B	DNAL4	EPC2	SATB2
ENTPD7	DVL2		IGF2BP1	PSTPIP1	DNAJB1	RPS13	THUMP3	EPC1	NAT10
SCAMP3	YWHAH		POLR3D	BCAS3	MYH9	DHX8	TIMM17A	NDUFS1	LRRFIP2
SPAG9	ARHGAP21		POLR3E	BCR	HELZ	TMPO	FAM171B	FAM160A2	PIP5K1A
HK2	SEC31A		POLR3B	STAT2	SNRPA1	PTK2	WASF3	MRGBP	LY6G5B
TWF2	TRIM25		MAP3K2	OBSL1	PRPF40A	RUNDC3A	MLLT4	HBB	BASP1
FAM206A	NAT2		POLR3K	USP1	CLASRP	EDC4	PUSL1	PBXIP1	AATF
UBR2	YWHAH		POLR3H	DSG1	PHACTR4	BIRC7	TSR3	SMAP2	CDK8
UBR1	KRT13		CALM1	MORF4L2	H1FO	TCEB2	NOP56	CCDC102A	NRF1
UBR4	HSD17B4		MPP3	RPS26	GAPDH	SYNRG	TBX3	CSNK2A2	AMOTL1
KCTD13	YWHAH		MPP1	BNIP3L	TXN2	TSLP	BRIX1	NAV2	SVIL
ZNF445	TRA2B		DNMT1	USP4	ENO1	Parp1	TLN1	KLHL8	PCBD2
KCTD10	PPP1R13B		DEAF1	RABGEF1	NKPD1	CTNNB1	BRPF3	HDAC2	MSH2
KRTAP10-9	PCNA		MAP3K4	WBP11	IGF2BP1	CORO1C	TMEM55B	EP400NL	USP4
ROBO2	FYB		FAM110A	SORD	CLU	ITGB3BP	GZF1	RNASE7	NIFK
WDR59	COPA		FAM110B	LGALS7	EP300	ACTBL2	SIPA1L1	VWA9	MSH6
UBC	VASN		NSFL1C	RPLP0P6	POLR2J	ARID4A	CEBPZ	SERPINB8	SPECC1
SLC19A3	DHFR1L		MAG1	TBL1XR1	PPP1CC	AACS	TIMM50	RBP2	RPRD1A
HIRIP3	ANXA7		ASRGL1	RPSA	MAPK9	SRF	RPL26L1	SERPINB2	GLYR1
FZR1	COPE		KLHDC10	GLIDR	LIME1	RRP8	YWHAH	BRAT1	MRPS15
RPL7	CARD11		CUL2	ERCC6L	C1orf27	UGT1A7	ZBTB2	CSNK2A1	MRPS14
MIOS	SYBU		LUC7L2	GAREML	IRS4	SMARCA4	TRAF3	H2AFV	CDADC1
CLTC	HGS		IARS	PREP	GJA9	HHT2	BANP	KRTAP10-9	MRPS11
KBTD7	UQCRCF51P1		TONSL	TMPO	IRS1	EIF2S3	PPAN-P2RY11	KRTAP10-1	MRPS10
GOLPH3	CASC3		CREB1	SNTB2	IRS2	EIF2S2	HOOK2	L3MBTL3	SORBS2

FIG. 5D

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
AKT1S1	HEATR1		TRIM23	DTX3	TCP1	KRTAP10-3	BEST1	ZKSCAN7	HIP1
CRMP1	TNF		SLC25A26	LDHAL6B	CDK3	CEBPA	DKC1	UBC	IQGAP1
ATG9A	PCNT		MDM2	EIF6	BABAM1	CEBPG	ORC2	KDM5A	RICTOR
UBXN6	PRKCQ		USP33	TXNL4A	ISY1	MYOD1	ORC1	VP572	NSMCE4A
UBXN7	TUBA4A		GPATCH1	PTPN21	SH3PXD2B	CEBPE	NLE1	ASPHD2	DDHD1
C3orf58	CYTH2		Ctnnb1	CHORDC1	Synj1	AQR	GTPBP4	NFKB1B	UNC119
SIRT5	CTNNA1		NIN	RAB5B	SH3PXD2A	PRPF19	LBX1	EP400	FYN
FAF1	ACTN1		SNRPD2	TLN2	XAB2	CPSF3	AR	FLG	RB1
ARPC2	ECT2		RNF185	TLN1	NEU3	MLLT6	ATN1	PTN	MED10
POLR2A	UTP14A		LIMA1	ATG5	RP11-343C2.12	CENPH	NR2E1	SHCBP1L	MED11
HIST1H2BB	PRPF38A		KIF5B	PCNA	PTK2	LSM12	LAMP2	HAUS4	MED12
SART1	SRSF2		MASP1	PIGA	SF3B4	NPAS2	EPHA10	NKAPL	MED13
GET4	TXNDC11		Slc25a4	HSPB1	SF3B1	RPL23	TRIP10	CPA4	MED14
ETV1	MYO6		UTRN	MCM5	RPRD1A	ALX4	KRTAP4-12	DCTN5	MED15
TAF6	PPP2R5A		KPNA2	MCM3	NFYB	KLF5	HIST2H2AB	LZTS2	MED16
TMEM65	MBD5		KPNA1	KRTAP26-1	FGD6	WDR36	HIST2H2AC	UBB	MED17
CDC27	MAD1L1		ZBTB21	SNRNP40	PFDN5	MED16	NF1	FAM118A	MED18
CDC26	RND2		DOCK8	RHPN1	IQGAP1	EIF4ENIF1	DPH1	MTFR1	MED19
TNFAIP1	STON2		Nbr1	PPP1CA	YWHAZ	SIPA1L1	NUDT21	EFHC1	CCT6A
RBPMS	POU3F3		Deaf1	ABCC2	DRG1	CNOT7	VAMP2	GATAD1	PACSIN3
TAF9	CREBBP		MED24	ILF2	HDGFRP3	PSMC5	HAP1	TRIM41	CCT6B
NUP153	C2CD5		GSKIP	ISL1	INPPL1	SIN3A	ECT2	PRDM14	INTS7
HTT	TIA1		PTPN11	PSMF1	PACRGL	SMURF1	RBM19	DEPTOR	KRI1
BTBD9	PDPK1		RICTOR	MFHAS1	YWHAQ	TRAF2	LIN54	IVL	SSNA1
IPO8	BOLA3		ZSCAN1	ZFAND6	RB1	SMARCB1	RPL36	CEP170P1	PSME3
IPO9	TPR		SMURF2	PUF60	HSPD1	ZNF7	WDR75	IPO8	CAMK2D
BUD31			USP48	CCDC158	YWHAH	PDIA6	MEAF6	IPO9	AP2A1
IPO7			SEN8	TPX2	HCLS1	PSME4	MELK	IPO7	CASC5
IPO5			JUN	AHCYL1	XRCC6	NR4A1	NOC3L	KDM1A	TUBA4A
RNF123			PPARGC1A	WWC2	CCT6A	PSME2	RPL30	POF1B	GNB2
ACTR2			NARS	WWC1	YWHAQ	sep-04	CSTF2	USP15	CALD1
MAPK14			PIAS1	LYZ	YWHAH	RTN2	TARBP2	ME1	MTFR1L
MAPK11			RBM39	DSC1	NDUFS6	MCM6	KIF13B	GADL1	DDX27
NPLOC4			MAP1B	GOLGA2	ANXA6	AR	SPTY2D1	LMNA	EDRF1
NCOR1			GBP2	KHK	EEF1A1P5	MCM3	ZNF92	TNPO2	NRIP1
TNPO1			UBA1	CREBRF	PSME3	SKIL	HCFC1	CYTH2	LIMCH1
NR6A1			SPICE1	IL36RN	PSME1	TMX3	KAT6A	CCDC105	ACTG1
TBC1D4			TP53	PRRC2B	CASC3	ALOX15B	MUT	HNRNPU	DYNLL2
TECR			MELK	P4HB	HIST1H3A	BRMS1L	WDR74	HIST2H2AC	FCHO2
HSPA12B			EIF4EBP1	PAG5	AP2A1	RBM14-RBM4	svp	HNRNPK	MYL6
HSPA12A			LRCH2	ATP2B1	AP2A2	CTNNA1	WDR76	HNRNPM	CCT4
NFKB1			PPP2R5D	EIF4G3	TUBA4B	RPL28		MAPK9	MYL9
CECR6			UBE2S	EIF4G2	ABI3	EIF4E3		ASH1L	SUGT1
ZGLP1			UBE2W	EIF4G1	CUL4A	SNW1		PDSS1	CALM1
ATP12A			NADK	FZR1	MAP4K1	RPL26L1		SYNE2	DNMT1
RAI1			SMN2	KRTAP10-3	NKTR	CASP3		PHLPP1	RORC
AMFR			BAG6	ADAM8	ARHGAP35	RPL38		TNFRSF13B	RORB
HIST1H1A			ADIRF	KRTAP10-7	TWISTNB	ABI2		TNFRSF13C	THRA
Dlg1			RPS2	GRB2	WIPF3	SRRM2		ZNF521	DLGAP1
YTHDC1			CTNND1	XRN1	WIPF2	NRIP1		ZNF529	NEXN
Dlg3			ARRB1	UBC	WIPF1	EZR		ZNF131	CLINT1
BSG			RPL36AL	KRTAP10-5	ACTG1	TBC1D10B		NUMA1	WDR62
Dlg4			BCAS2	RPL8	NISCH	PSAT1		TEX35	WDR60
EMP2			RBM8A	RFXANK	KRT32	NONO		CLPB	LSS
PIAS4			DHX58	EP400	KRT35	Grip1		FBXO39	ZNF207
PSMB6			ZHX1	DNM2	KRT34	TIMM13		CAND2	BRCA2
FBL			CBY1	FLG	KRT36	ACTL6A		PDZD11	TRIM29
NUMA1			MARK4	PLXNB1	C7orf55	G3BP2		CTU2	ACOT7
HAX1			MARK1	FATE1	RAPGEF1	ATF5		RFTN1	MTPAP
DCAF13			MARK2	TERF1	SNRNP200	ATF4		UBE2G1	SHMT2
DDOST			MARK3	CRMP1	CALM3	CMTM5		SIN3B	USP36
CAND1			HIST2H2AA3	LZTS2	MAP3K1	CALCOCO2		SIN3A	FGFR1
PLOD2			MSH2	KLHL36	BCLAF1	ATF3		HOOK2	DZIP3
SLC9A3R2			SRC	KIAA0368	PARD6A	POU2F1		HOOK3	MORN3
SIN3B			EPB41L3	IFT74	DLGAP1			HOOK1	LIMA1
NR3C1			USP4	SGTA	ERBB2			DMKN	MYLK
MADD			NDUFA9	TRIM46	SHC1			ARMC8	RAI14
Cask			TPD52L2	MTFR1	PNKP			NDEL1	KIF22
MAP7D1			IGSF21	SART1	TRIM27			NF1	NKAP

FIG. 5E

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miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
USP11			UCHL5	ETV6	SLC25A6			BRAP	NUCKS1
HSPA14			LGALS1	CEP170P1	SLC25A5			CCDC120	MYO5C
TXNDC11			QARS	LRRC15	CHERP			TMEM39A	MYO5B
ATF1			UCHL1	BTBD9	GPATCH8			ACTL6A	MYO5A
ATF2			UCHL3	BTBD8	DNAJA3			TUBA1A	CD109
			SGK3	ANKEF1	PTPN18				MED29
			FARSB	KDM1A	INPP5D				MED28
			FIS1	HNRNP1	GAREM				PNRC1
			C14orf1	NCOR1	SYK				MED21
			PDE4D	SNRPF	PTPN12				MED20
			PIIB	CNKSRI	PTPN11				MED23
			DTX3	GCN1L1	INCA1				MED22
			BIRC3	SNRPG	RBBP6				MED24
			BIRC2	PDCD4	KIT				MED27
			CYCS	MAPK9	TTC14				MED26
			FOXO1	POMP	NKAP				NOP14
			MAP4	RCC1	KPNA2				NOP16
			SPTBN4	DTNB	SYNM				XRCC1
			Krba1	PHLPP2	FAM98B				SEC16A
			CLEC3B	PHLPP1	SKAP2				sep-07
			DPP8	SYNE4	DOCK1				FAM13A
			DPP9	VPS26A	GAB2				ZSCAN1
			LPCAT1	VPS36	GAB3				sep-02
			EYA1	PKD1	DOCK4				SRSF5
			MID1IP1	ID2	GAB1				STIL
			RBCK1	GLB1	ARHGAP9				AHNAK
			ILKAP	NXT2	XRCC1				SRSF9
			PPP6R3	CSE1L	CRK				TCP1
			Gm4779	MKI67	XRCC5				MKS1
			PPP1CA	ZNF250	LY86				JUP
			AQR	CHGB	AP2S1				NPPA
			CYC1	STRA13	SRSF6				COBL
			PRPF19	ACAD11	SRSF1				UBA1
			Dvl1	COTL1	STAT5B				CORO2A
			MAPT	UBQLN4	AGTRAP				GPHN
			ISY1-RAB43	TTL12	AHNAK				UBE2I
			UFD1L	SIN3B	SRSF9				RBFOX2
			BCL3	LDHA	VPS37B				MRPS28
			CKAP5	SIN3A	PCDH85				GNAS
			DARS	SLC39A10	DNAJB11				MED13L
			SRP9	PABPN1	RBM33				MRPS24
			AKT2	TRAF6	MAP1A				PRTFDC1
			RBPJ	TRAF7	PRKAB1				CDC14B
			MICAL1	USP15	HOMEZ				MRPS21
			FAM193B	SNRPB	PARP1				CAMKK2
			MYC	SSBP3	UBA1				POLE2
			AURKA	NPM1	PTPN1				PHF8
			ENTPD6	NAGK	PTPN6				PHF2
			DDIT4	SEC22B	TNFRSF1A				RASIP1
			SOD1	DIS3	WARS				MYO1E
			KCTD11	UNC45A	RPAP2				DSN1
			SMAD1	ZBTB43	ARHGEF7				MYO1B
			GIPC1		TOP3A				RPS2
			UBR1		SYN1				FBXO7
			UBR5		NADK				RPL36AL
			CRCP		BAG1				RAF1
			MLLT4		CTDP1				BTBD10
			PCGF6		LAX1				NUSAP1
			EEF1G		KRT2				CEP162
			GSK3B		KRT1				BMP2K
			INADL		KRT7				TCEB3
			UBC		KRT5				RABEP1
			RPL9		KRT4				DSG2
			DCLK1		CYP251				NMNAT1
			FEN1		PSTPIP2				KDR
			SLC25A38		KRT9				GOLGA5
			PTN		KRT8				SRC
			CHD3		A2M				RABGEF1
			NMD3		BCR				CCDC36

FIG. 5F

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
			BEX1		JMJD4				SORD
			TUBA1A		MICAL1				ZC3HAV1L
			NOTCH1		KRT81				PAWR
			FATE1		KRT82				CCDC132
			PLEKHA7		KRT83				MYL12A
			UBXN6		KRT85				MRPS16
			EPM2A		KRT86				ARPC5L
			NCOA3		SNX18				EIF2AK4
			PGM1		KRT6A				MRPS26
			GYS1		ND4				PALLD
			POLR2A		SRC				STX12
			MIA3		CD59				MYO19
			TMEM44		RPS20				WDR19
			POLR2H		PHC2				PPIA
			ANKRD28		WBP11				EFHD2
			STAT1		SRM				MRPS25
			USP51		CD180				ANTXR1
			SNCA		WAS				PPP1R1C
			FUCA1		ZMAT1				MRPS23
			NRBP1		MYL12B				CORO1B
			KDM1A		MYL12A				CORO1C
			STAMPB		GAREML				MAP6
			SDCBP		E2F2				NOC4L
			Spice1		MAGOH				SPTBN2
			CWF19L2		WDR12				YES1
			ZNF746		RPRD1B				RNF170
			NANOG		PPIG				NAP1L1
			FZD5		PPIE				RPL26
			TBK1		BLNK				RPL22
			LGALS14		PDE4D				MRPS7
			AP2M1		ASAP1				MRPS6
			MAPK1		ASAP2				TPRG1
			HNRNPM		OCRL				ATP5G1
			NFKB1		MAP4K3				STRN
			SNRNP70		MAP4K5				ANXA2
			PRUNE		CUTA				LRCH2
			NUB1		BPGM				MRPL19
			SYDE1		CYFIP2				GLTSCR2
			TPD52		KIRREL				PPP1CB
			SYNE1		MAP2				PPP1CC
			PHLPP1		AEBP1				PPP1CA
			SYNE4		PSMD13				NOC3L
			CRNKL1		SPTBN1				PICALM
			ZCRB1		PTPN23				ZNF512B
			MTF2		HIST4H4				NGDN
			SREBF1		MLLT4				TMOD1
			PRKACA		KRT33B				TMOD3
			RNF144A		AMBP				LZTFL1
			HSP90AA1		NAP1L5				GSN
			ZNF135		FAU				CCDC102A
			KCTD2		NUTM2F				CCDC88A
			KCTD6		SYNJ1				ANAPC16
			ARL3		HNRNPA2B1				DDX31
			ARL2		SYNJ2				WHSC1L1
			PFKFB4		EYA3				CYBRD1
			RIPK1		ANXA2				HSP90AB1
			Map3k11		PEAK1				ARHGAP21
			CACYBP		MSI2				MICAL3
			U2AF2		KRT10				FLII
			FAM83D		IK				CSNK2A1
			CREB3L3		Dnm1				NEK9
			TSR1		NIF3L1				NARFL
			GLI2		DYNC1H1				LYN
			GLI1		FLNA				ZAP70
			PIM2		MCM8				AURKB
			CLASP2		FAM154B				NUF2
			TRAF6		CASP2				HK2
			PDIA5		ARAP1				MYO1C
			PDIA3		PPP1CA				ZNF362

FIG. 5G

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
			DNMT3L		FAM9B				MRPS2
			AR		SRRM2				TSPAN2
			USP14		RPA1				CEBPZ
			USP15		DRD3				C12orf40
			ALDH1B1		PON2				ATG2B
			ABCC10		EIF4A3				UBR5
			TXNDC17		TOM1L1				TWF1
			AARS		FASLG				TWF2
			RPL30		WDR83OS				BARHL1
			UPF3B		HCVgp1				PPP2CA
			GRIN2A		MDFI				ARPC1B
			ATF3		LAT2				FZR1
			ACTL6B		DARS				ELFN2
			DNM1L		PBXIP1				CCDC86
			BAP1		NKX2-5				L3MBTL3
			Vta1		NTRK1				GRB2
			Prox2		HSP90AB1				ZKSCAN4
					SMAD4				CCNC
					TTYH2				CCDC93
					LIG3				SPC25
					MYC				UQCC2
					Mta1				MACF1
					Mta3				PHF21A
					CD28				H2AFY
					SOD1				SPECC1L
					CD22				DEK
					ALOX5				CLTA
					RANGAP1				CLTC
					DPPA4				CLTB
					TSPAN2				CCHCR1
					YWHAB				PNMA3
					RBP4				THAP11
					PRAP1				JMY
					HSPG2				HAUS6
					UBR4				HAUS7
					SOCS4				HAUS5
					SOCS1				HAUS3
					EEF1G				MED12L
					EEF1D				TRO
					MST1R				SAMD1
					CD2AP				PIK3R1
					GRB2				PCBP1
					HUNK				LZTS2
					UBC				ZFC3H1
					GPALPP1				TROAP
					CCT6B				MRPL13
					UQCC2				SDAD1
					HP				RAB3GAP1
					RPL5				ARPC3
					FMN1				ARPC2
					NR3C1				MED30
					FH				MED31
					DNM1				ARPC4
					PPP1R21				DSTN
					CLTC				PLEC
					DNM2				ITPR2
					PNMA5				ITPR3
					NCKAP1				KIAA1109
					TP53RK				MISP
					LRRK1				PEX5
					AP4S1				TLK2
					FAM175B				VAV1
					CMAS				TNFAIP1
					PIK3R3				RBPMS
					PIK3R2				STON2
					PIK3R1				SPC24
					LZTS2				ACTR3
					SH2D4A				ACTR2
					SH2D5				CFL2

FIG. 5H

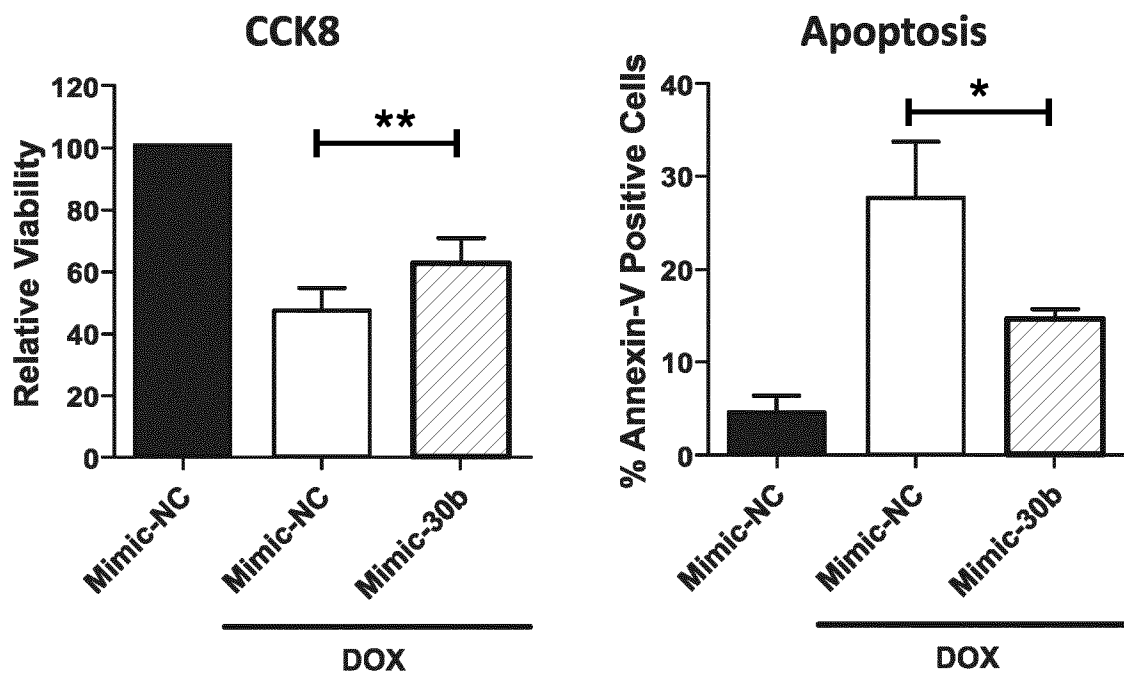
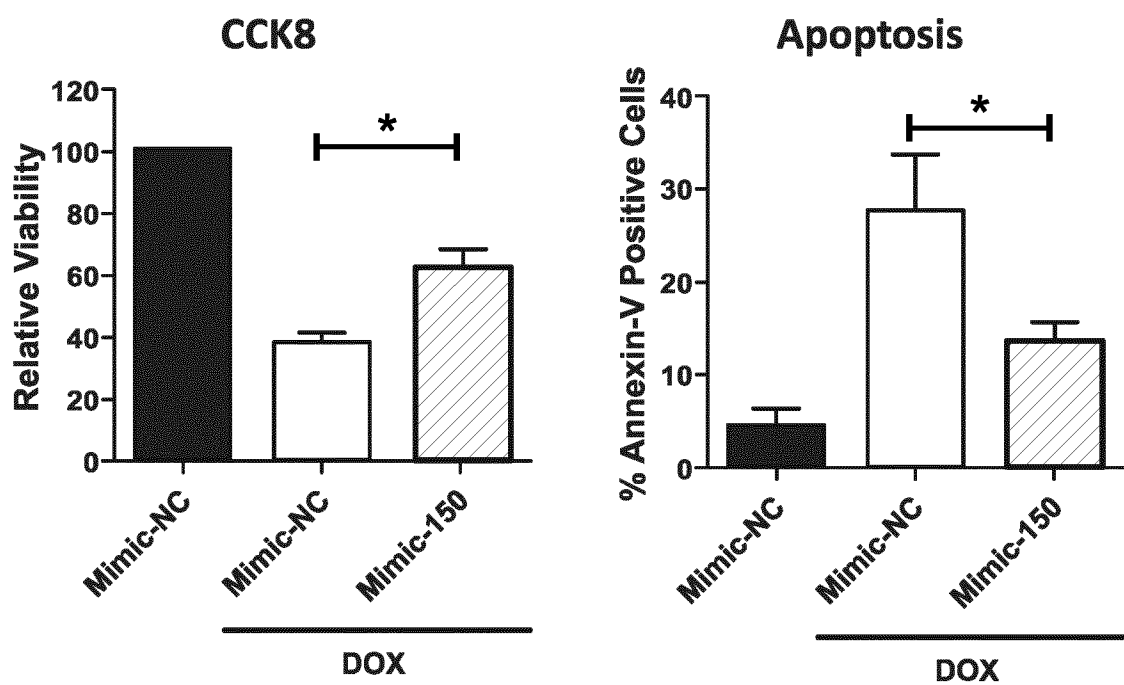
miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
					LNX1				KDM1A
					LMX1A				ACE
					ARPC4				STOM
					POLR2E				DIABLO
					POLR2D				ABL1
					POLR2G				GNAI2
					POLR2F				NCOR1
					PLEC				GNAI1
					DAG1				SCML1
					POLR2C				PIK3C2A
					POLR2B				MRPS34
					POLR2M				MRPS33
					POLR2L				AP2M1
					POLR2I				PPP1R12A
					KIF3A				PPP1R12B
					VCP				SRD5A1
					VAV3				SNRNP70
					VAV2				TUFT1
					USP53				HELLS
					SHBG				SEL1L
					HTT				HMGA1
					RBM22				BCOR
					ELMO2				BCAP31
					BUD31				YTHDC1
					GRPEL1				ACTRT1
					GPANK1				ARHGAP11A
					WBSCR27				WIZ
					STAMBP				AMOT
					EPHA2				RPS12
					PIK3AP1				UTP3
					LY6G6F				ZNF318
					ABL1				DNM2
					NPLOC4				RHOXF2
					SHKBP1				LCA5
					IKZF3				MSN
					TEC				FAM83H
					HNRNPU				ANKHD1
					REPS2				CACTIN
					AP2M1				RAB36
					HNRNPK				RAB34
					GPN3				BCL2L11
					PPP1R12A				C14orf80
					GPN1				TSR1
					HNRNPC				CPNE1
					HNRNPD				RPS19BP1
					REEP6				AHDC1
					CECR2				KCTD20
					NKD2				DAPK3
					POMP				TSSC1
					ARL6IP4				PLS1
					ABI3BP				ESF1
					TCEAL8				TFAM
					CRNKL1				HOOK1
					FHOD1				ACAP1
					FAAH				LUZP1
					SOS2				CFL1
					SOS1				PLEKHG3
					SLAIN2				ACTN1
					SMU1				ACTN4
					MET				RPL36
					APLN				PRPF38A
					HSP90AA1				RNF169
					BRE				UNC45A
					CLPX				IMMT
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					PPCDC				PTRF
					RPS19				
					TOMM22				
					PDCD6IP				

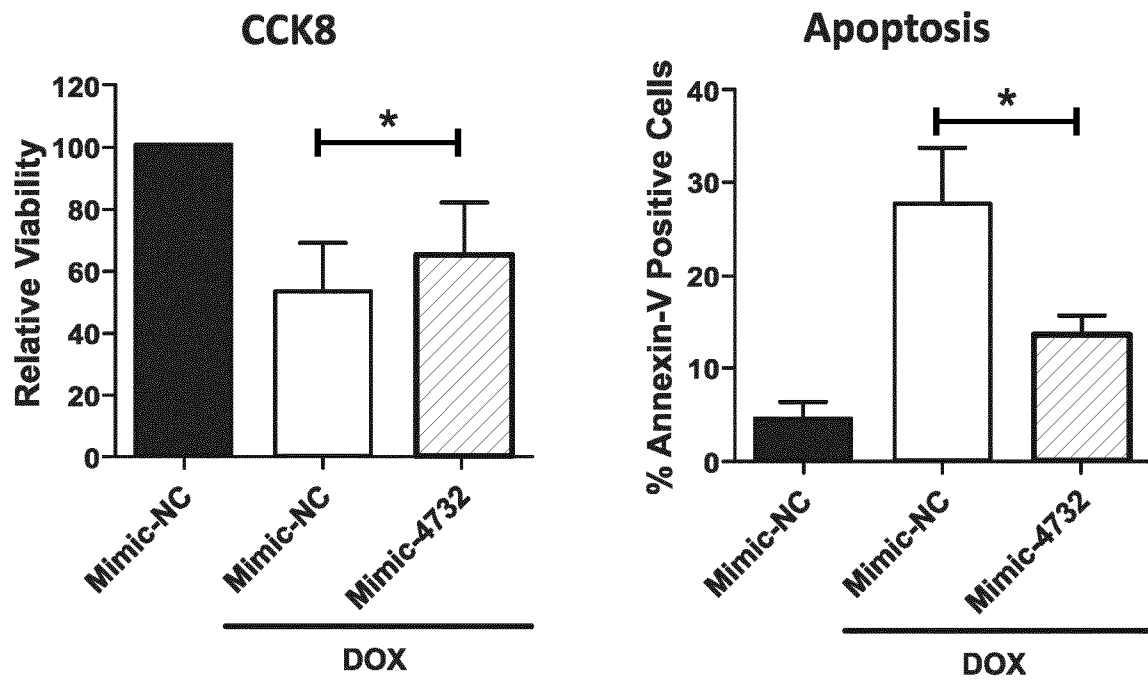
FIG. 51

miR-150-5p	miR-215-5p	miR-192-5p	miR-92b-3p	miR-486-3p	miR-16-5p	miR-148a-3p	miR-22-3p	miR-30b-5p	miR-30c-5p
					HSPA1B				
					PDCL				
					HSPA1L				
					TXN				
					UBASH3B				
					THRAP3				
					AQR				
					PRPF19				
					TRAT1				
					ARHGAP32				
					DOK3				
					DOK1				
					PXN				
					TTL12				
					TF				
					USP6NL				
					SH3KBP1				
					SNTA1				
					RABGEF1				
					CLASP2				
					MLXIPL				
					ORC2				
					ACAP1				
					ESD				
					FBF1				
					SHANK3				
					RASA1				
					TAB1				
					CD164				
					TUBA1C				
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					C1orf94				
					ACTL6A				
					PTPRA				
					MYOZ1				
					PTPRJ				
					GSTK1				

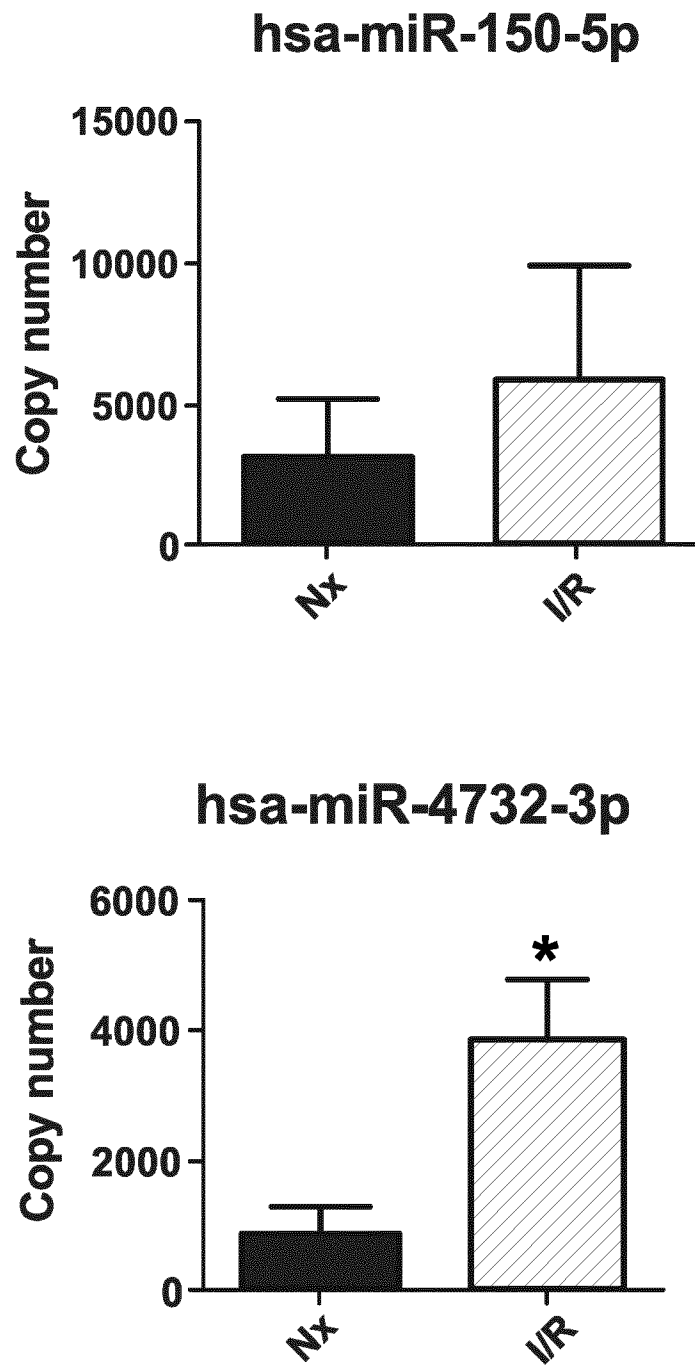
FIG. 5J

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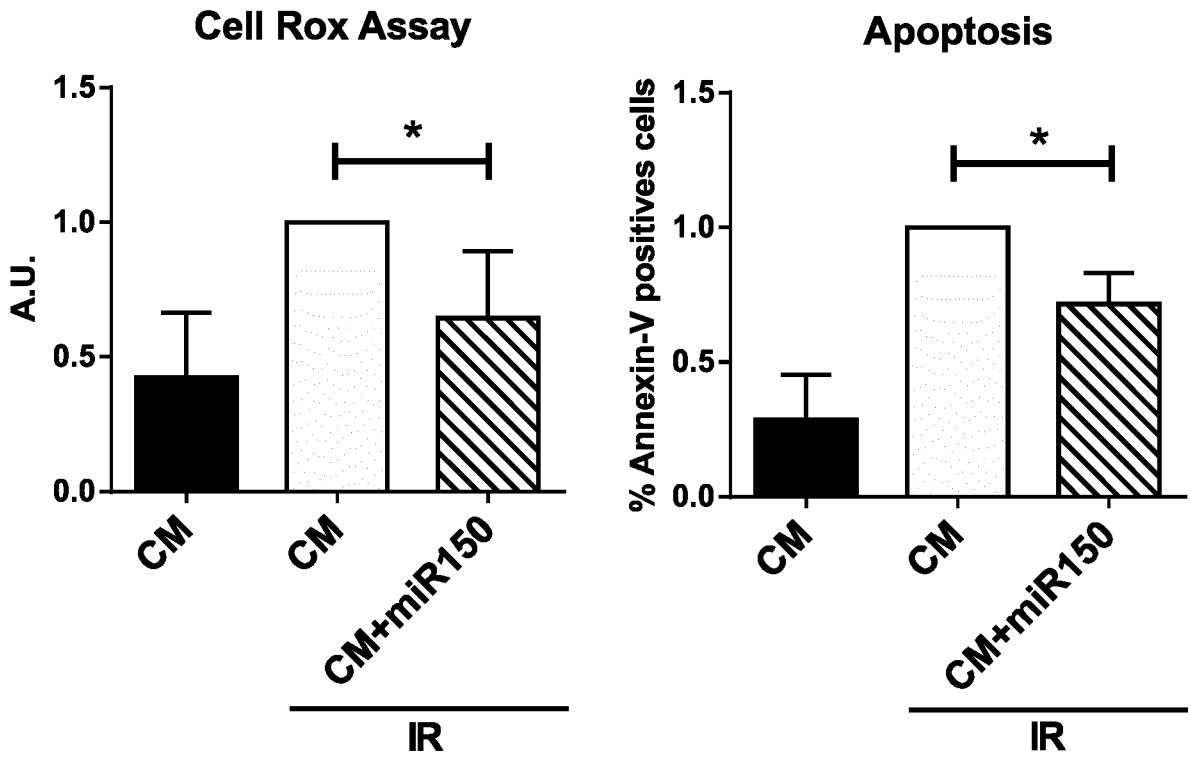
hsa-miR-30b-5p**hsa-miR-150-5p****FIG. 6A**

hsa-miR-4732-5p**FIG. 6B**

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**FIG. 7**

hsa-miR-150-5P



hsa-miR-4732-3p

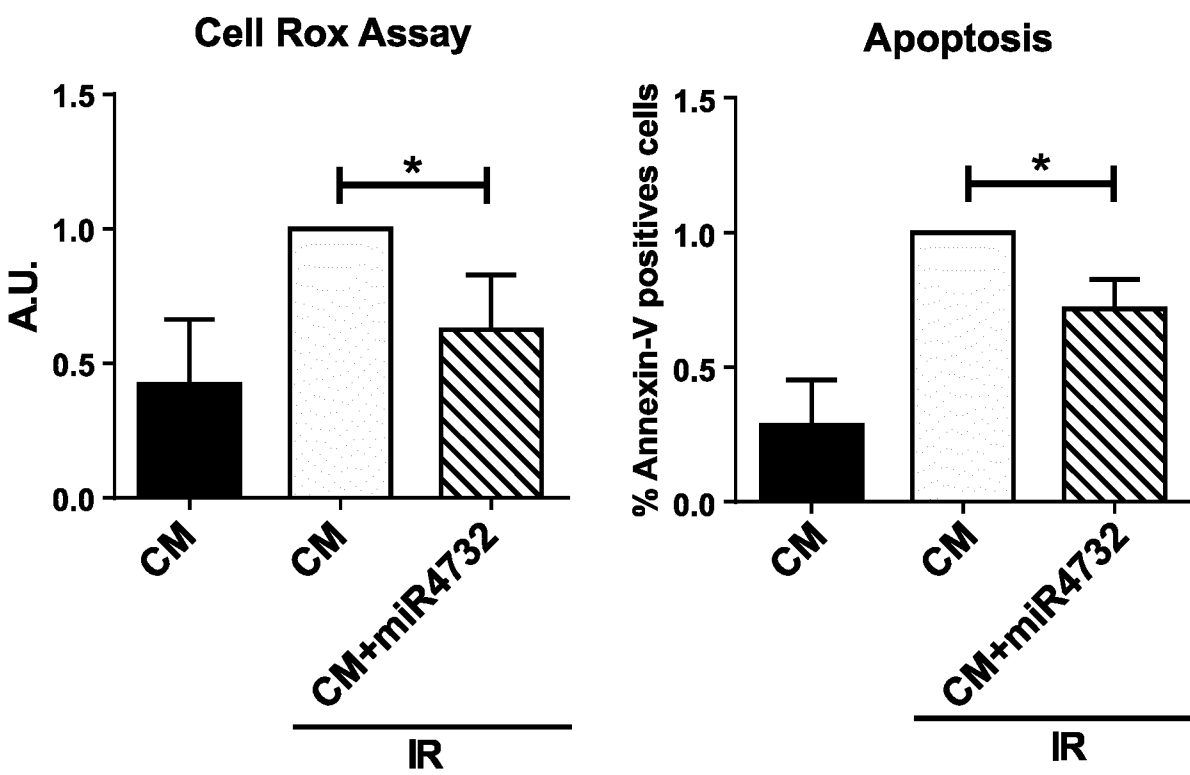


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/085388

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6886
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RUGGERI CLARISSA ET AL: "Role of microRNAs in doxorubicin-induced cardiotoxicity: an overview of preclinical models and cancer patients", HEART FAILURE REVIEWS, KLUWER ACADEMIC PUBLISHERS, DORDRECHT, NL, vol. 23, no. 1, 25 September 2017 (2017-09-25), pages 109-122, XP036397539, ISSN: 1382-4147, DOI: 10.1007/S10741-017-9653-0 [retrieved on 2017-09-25] ----- -/--	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

11 March 2020

Date of mailing of the international search report

19/03/2020

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Cornelis, Karen

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/085388

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHAUDHARI UMESH ET AL: "MicroRNAs as early toxicity signatures of doxorubicin in human-induced pluripotent stem cell-derived cardiomyocytes", ARCHIVES OF TOXICOLOGY, SPRINGER, DE, vol. 90, no. 12, 3 February 2016 (2016-02-03), pages 3087-3098, XP036096455, ISSN: 0340-5761, DOI: 10.1007/S00204-016-1668-0 [retrieved on 2016-02-03] the whole document	1-7
A	----- WO 2012/010905 A2 (UNIV COVENTRY [GB]; MADDOCK HELEN [GB]) 26 January 2012 (2012-01-26)	1-7
A	----- ZHU HAI-JUAN ET AL: "Specific MicroRNAs comparisons in hypoxia and morphine preconditioning against hypoxia-reoxygenation injury with and without heart failure", LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 170, 2 December 2016 (2016-12-02), pages 82-92, XP029904725, ISSN: 0024-3205, DOI: 10.1016/J.LFS.2016.11.028	1-7
A	----- SONG LINA ET AL: "Role of non-coding RNAs in cardiotoxicity of chemotherapy", SURGICAL ONCOLOGY, BLACKWELL SCIENTIFIC PUBL., OXFORD, GB, vol. 27, no. 3, 19 June 2018 (2018-06-19), pages 526-538, XP085472328, ISSN: 0960-7404, DOI: 10.1016/J.SURONC.2018.06.003	1-7
A	----- KASEY J. LEGER ET AL: "Circulating microRNAs: Potential Markers of Cardiotoxicity in Children and Young Adults Treated With Anthracycline Chemotherapy", JOURNAL OF THE AMERICAN HEART ASSOCIATION, vol. 6, no. 4, 5 April 2017 (2017-04-05), XP055651614, ISSN: 2047-9980, DOI: 10.1161/JAHA.116.004653 cited in the application	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/085388

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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