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(54) Title: METHODS OF IDENTIFYING COMPONENTS OF A BIOLOGICAL PATHWAY AND USE OF SAID COMPONENTS IN REGULATING DISEASES ASSOCIATED WITH ALTERED CELL PROLIFERATION

(57) Abstract: A method of identifying components of a biological pathway is disclosed. The method comprises selecting a transcription factor and a microRNA pair which regulate a common gene, the transcription factor and the microRNA being the components of the biological pathway. Methods of treating diseases associated with cell proliferation using components identified according to the method above and pharmaceutical compositions comprising same are also disclosed.



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METHODS OF IDENTIFYING COMPONENTS OF A BIOLOGICAL PATHWAY AND
USE OF SAID COMPONENTS IN REGULATING DISEASES ASSOCIATED WITH
ALTERED CELL PROLIFERATION

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FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of identifying components of a biological pathway. In addition, the present invention relates to use of identified components for regulating diseases associated with altered cell proliferation.

MicroRNAs (miRs) are short RNAs that post transcriptionally regulate messenger RNAs. Two main mechanisms for such effects are degradation of the target mRNA, and inhibition of its translation. In recent years considerable progress within multiple genomes was obtained in the experimental identification of genes encoding for miRs, and in tools for the identification of target genes of miRs, based on miR sequences and the sequence of the targets' 3' untranslated regions (UTRs). Compared with the regulation of transcription, the study of the regulatory networks spanned by miRs is only at its beginning. A lot is known about the main players of transcriptional regulation and the interactions between them. Transcription factors (TFs) are well characterized and promoter binding motifs are available in a diversity of species. The combinatorial interactions between TFs have been explored as well as the global level properties of the transcription regulatory network. In addition, the local structures of the network have been intensively investigated. It was found in several species that the transcription regulatory network may be decomposed into elementary building blocks, or network motifs, that recur in the network more than expected by chance, and that these motifs likely perform local "computations," such as the detection of signal persistency or the coordinated gradual activation of a set of genes.

When it comes to posttranscriptional regulation, and in particular to the miR world, most of the parallel knowledge is lacking. While evidence exists for the occurrence of many miRs in multiple genomes, their targets are predicted with relatively limited accuracy. Furthermore, there is a lack of knowledge about the structure of the miR regulatory network, and about the potential interface between this network and the transcriptional one. Similarly to TFs, miRs are expected to work in combinations on their target genes. The target specificity-determining site of the miRs is often short (seven to eight nucleotides), hence some genes that contain a match to a single miR in their 3' UTRs may represent false positive assignments. Thus combinatorial interactions among the miRs

are probably necessary to allow specific targeting of genes targeted by each miR. As in the realm of transcription regulators, combinatorics may also have the advantage of allowing multiple sources of information, each represented by a single miR, to be integrated into the regulation of individual transcripts.

5 Since TFs regulate mRNA production, and miRs regulate transcript stability and its translation, an attractive possibility is that miRs and TFs cooperate in regulating shared target genes. This may be advantageous since a gene that is regulated through multiple mechanisms may be tuned at a level of precision that is higher than what may be obtained by either mechanism alone.

10 The tumor suppressor p53 is a sequence-specific transcription factor (TF) that exerts many of its downstream effects by activating gene transcription. P53 is considered a central regulator of cell fate decisions. Activation of p53 can induce several cellular responses, including cell-cycle arrest, senescence and apoptosis. Thus, absence of functional p53 predisposes cells to neoplastic transformation. Accordingly, mutations of
15 this gene are highly common in human cancers. Even though p53 is known as a transcription factor, additional transactivation-independent functions of p53 contribute to its tumor suppressive activity, including protein-protein interactions with additional transcription factors and other cell fate regulators. The importance of transcription regulation by p53 is exemplified by the fact that most p53 tumor-derived mutants are
20 defective in DNA binding and incapable of transactivation. In addition to its capability to induce gene transcription, p53 activation results in extensive gene repression. Direct and indirect transcriptional repression by p53 is considered important for its tumor suppressive functions, such as induction of cell-cycle arrest and apoptosis.

25 As well as transcription factors, microRNAs are also known to regulate cancer-related processes such as apoptosis, proliferation and differentiation. Deregulated miRs were suggested to exert their function in cancer via silencing of key cell fate regulators, as shown for let-7 and Ras (Johnson et al, 2005, Cell 120: 635-647), as well as for miR-106b and p21 (Ivanovska *et al*, 2008, Mol Cell Biol; Petrocca *et al*, 2008, Cancer Cell 13: 272-286).

30 Several studies have implicated p53 in the regulation of miR expression (Chang et al, 2007, Mol Cell; He et al, 2007, Nature; Kumamoto et al, 2008, Cancer Res, In Press; Raver-Shapira et al, 2007, Mol Cell; Tarasov et al, 2007, Cell Cycle 6; Xi et al, 2006, Clin Cancer Res 12: 2014-2024). These studies exploited various high throughput methods to identify p53-regulated miRs in several cellular systems with differential p53 status.

Although the resulting candidate lists from each study differed considerably, probably due to differences in the cellular contexts and p53 activation signals, all studies identified members of the miR-34 family as direct transactivation targets of p53. In line with p53 function, induction of miR-34 family members was suggested to mediate cell-cycle arrest, apoptosis and senescence. Importantly, none of these studies focused on miRs whose expression negatively correlated with p53 activation, and who are likely repressed by this tumor suppressor.

Many miRNAs have been shown to be overexpressed in various tumors; and some have been shown to possess oncogenic functions. For example, miR-106a, miR-17-5p, miR-20a and miR-155, as well as miR-92, were reported to be commonly overexpressed in solid tumors (Volinia et al, 2006, Proc Natl Acad Sci U S A 103: 2257-2261). Members of the miR-17-92 polycistron are overexpressed in lymphomas as well as in lung and colorectal carcinomas (He et al, 2005, Nature 435: 828-833; Schetter et al, 2008, Jama 299: 425-436), and were shown to accelerate tumor growth (O'Donnell et al, 2005, Nature 435: 839-843). Finally, miR-155 was reported to be specifically overexpressed in several types of B-cell lymphomas (Eis et al, 2005, Proc Natl Acad Sci U S A 102: 3627-3632) and to predict poor prognosis in lung cancer (Yanaihara et al, 2006, Cancer Cell 9: 189-198).

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of identifying components of a biological pathway, the method comprising selecting a transcription factor and a microRNA pair which regulate a common gene, the transcription factor and the microRNA being the components of the biological pathway.

According to an aspect of some embodiments of the present invention there is provided a method of treating a hyperproliferative disease in a subject, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide agent capable of down-regulating at least one microRNA selected from the group consisting miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2*, hsa-miR-19b-1* miR-15b, miR-16, hsa-miR-92a-2*, and hsa-miR-92a-1* into the subject, thereby treating the hyperproliferative disease.

According to an aspect of some embodiments of the present invention there is provided a method of treating a degenerative disease in a subject, the method comprising administering to the subject a therapeutically effective amount of at least one microRNA selected from the group consisting of miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2*, hsa-miR-19b-1* miR-15b, miR-16, hsa-miR-92a-2*, and hsa-miR-92a-1* into the subject, thereby treating the degenerative disease.

According to an aspect of some embodiments of the present invention there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active agent at least one microRNA selected from the group consisting of miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, miR-15b and miR-16.

According to some embodiments of the invention, the transcription factor and the microRNA pair are listed in Tables 5-8.

According to some embodiments of the invention, a gene encoding the microRNA comprises a binding site for the transcription factor and/or a gene encoding the transcription factor comprises a binding site for the microRNA.

According to some embodiments of the invention, the transcription factor and the microRNA pair are listed in Table 9-11.

According to some embodiments of the invention, the transcription factor and the microRNA pair are listed in Figure 4.

According to some embodiments of the invention, the transcription factor regulates a transcription of an additional transcription factor, the microRNA comprising a binding site for the additional transcription factor.

According to some embodiments of the invention, the transcription factor and the microRNA are listed in Tables 12-14.

According to some embodiments of the invention, the hyperproliferative disease is cancer.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification,

including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIGs. 1A-B are graphs illustrating miRs and Target Genes in the TargetScan Dataset. (Figure 1A) Distribution of the number of different miRs regulating each target gene in the TargetScan dataset. The thick red line represents the distribution in the original dataset, while each of the thin blue lines represents the distribution in one of the column-randomized matrices. The matrix contains only genes with at least one predicted site in their 3' UTR. In each randomization, the assignment of miRs to their targets was shuffled, keeping constant the number of targets per miR. (Figure 1B) Distribution of number of targets per miR in the TargetScan dataset. The original distribution is depicted on thick red line, while each blue thin line represents the distribution in one of the 100 row-randomized matrices, which preserves the distribution of number of miRs targeting each gene.

FIGs. 2A-B are graph illustrating the distribution of the density of miRs in the 3' UTRs of target hubs (thick red line) and all the genes (thin blue line) in the TargetScan dataset (Figure 2A) and in the PicTar dataset (Figure 2B). All genes included in this figures have at least one miR site predicted in their 3' UTR. The log10 densities were binned into bins of 0.1, and relative frequencies were plotted.

FIG. 3A is a representation of the TargetScan miR co-occurrence network, at FDR level of 0.05. A node represents a miR and an edge connects between pairs of miRs with significant rate of co-occurrence. The nodes in the figure are arranged from most highly connected on the top, to most lowly connected, on the bottom.

FIGs. 3B-C are graphs illustrating the degree distribution in the TargetScan (Figure 3B) and PicTar (Figure 3C) miR combinatorial regulation network (co-occurring miR pairs that passed FDR of 0.05).

FIG. 4 is a representation of network designs in the miR–TF Coregulation Network. The figure depicts the analyzed network motifs in the TargetScan and PicTar dataset, with the use of TF binding sites in RefSeq genes promoters of 10 kb for both networks, and 5 kb for the PicTar network. The figure depicts, for each network motif, its architecture, the number of times it appears in each of the networks, the *p*-value and *z*-score for its over representation in the network (as described in Materials and Methods), the total number of RefSeq genes that are regulated by this type of network design, and an example. *For the first design, the coregulating miR–TF pair, the range of hypergeometric *p*-values of pairs that passed FDR and are considered significant are stated, and in brackets the FDR *p*-value of these pairs using the randomization co-occurrence test. **in addition, *z*-scores for significant pairs were calculated based on the co-occurrence edge-swapping randomization model (see Materials and Methods of Example 1).

FIGs. 5A-C are graphs illustrating tissue Expression Correlations between miRs and TFs. miR tissue expression in brain, liver, thymus, testes, and placenta were taken from Barad O, et al. (2004), Genome Res 14: 2486–2494; mRNA tissue expression was taken from Su et al., (2004) Proc Natl Acad Sci U S A 101: 6062–6067. (Figure 5A) Background distribution of all possible miR–TF pairs for which expression profiles can be derived. (Figures 5B, C) Normalized histograms of correlation coefficients; the same distribution as in (A) was made, yet only for significantly co-occurring miR–TF pairs (red), and FFLs (green) in the PicTar (B) and TargetScan (C) networks. The figure shows the proportion of the various correlation coefficients divided by the background distribution depicted in Figure 5A.

FIGs. 6A-B are graph illustrating miR Binding Sites in Target Hub Genes in the TargetScan and PicTar Datasets. Mean number of miRs targeting each of the genes that are target hubs (red bar), in the entire set of analyzed genes (green) and a distribution of that mean in random gene sets with the same (or very similar, see Materials and Methods) distribution of 3' UTR lengths as the target hubs (blue) in (Figure 6A) the TargetScan dataset and (Figure 6B) the PicTar dataset. For elaborated procedure see Materials and Methods.

FIG. 7 is a graph illustrating the distribution of number of miRs per cluster. As seen, ~82 % of the 301 clusters contain a single miR.

FIGs. 8A-C are graphs illustrating an analysis of miR clusters in the Human Genome. (Figure 8A) Distribution of distances between all neighboring pre-miR genes in the human genome. (Figure 8B) Distribution of tissue expression correlations between

pairs of miRs: all possible pairs in the data (thin blue line) and pairs of miRs which reside in shared clusters (thick red line). In the inset are shown tissue expression correlations between pairs of miRs in the same genomic clusters vs. distances between them. (Figure 8C) Distribution of number of conserved TFBS 30 kb upstream of the 5' most nucleotide in each miR clusters. Conserved TFBSs were taken from UCSC hg17.

FIG. 9 is a graph illustrating the distribution of a number of conserved TFBS 30 kb Upstream of TSS of RefSeq Protein-Coding Genes.

FIGs. 10A-F are graphs and photographs illustrating the establishment of the WI-38 system. WI-38 primary human fibroblasts were infected with a retrovirus encoding for the p53-inactivating peptide, GSE56. These cells (GSE) and their active p53 counterparts (NEO) were treated with the DNA damaging agent doxorubicin as well as grown until the onset of replicative senescence. Figure 10A: Western blot depicting p53 and p21 following doxorubicin treatment. p53 was stabilized and activated its target gene p21 in the NEO cells upon treatment. In the GSE cells, p53 was stabilized in its inactive form already at basal levels by GSE56, a 15 kDa peptide detected by the H-47 anti-p53 polyclonal antibody. The p21 protein was not detectable in the GSE cells at basal levels, nor was it induced upon DNA damage, indicating of a complete inactivation of p53 transactivation activity. Figures 10B-C: Introduction of the GSE56 peptide at passage 20 resulted in accelerated growth rate (Figure 10C) and delay in replicative senescence, as indicated by the reduction of senescence-associated β -galactosidase (SA- β -Gal) staining (Figure 10B). Figure 10D: Cell cycle analysis demonstrates that both DNA damage and replicative senescence resulted in a sharp p53-dependent cell cycle arrest. Figure 10E: QRT-PCR analyses of p21 mRNA levels demonstrated that p53 transactivation activity was significantly induced upon both DNA damage and replicative senescence, and was completely abolished by the introduction of GSE56. Figure 10F: QRT-PCR analyses of cdc20, a p53-repressed gene that participates in cell-cycle progression. To conclude, an isogenic pair of primary human cell cultures was created that display p53-dependent application of p53-activating stress.

FIG. 11 is a representation of the 'p53-repressed miR cluster'. Primary WI-38 cells (Con) and WI-38 cells were infected with the p53-inactivating peptide GSE56 (GSE) and analyzed for miRNA expression at early passage (Young), after doxorubicin treatment (0.2 μ g/ml, 24 hours) of early passage cells (Dox), and at the onset of replicative senescence (Old).

FIGs. 12A-B are graphs illustrating that inactivation of p53 by GSE56 (GSE) or shRNA (p53i) in three different human primary fibroblasts delays replicative senescence and attenuates the repression of miRs and their hosts upon senescence. Figure 12A: Growth curves for the human primary fibroblasts WI-38 and IMR90 and for the prostate cancer-associated fibroblasts (CAFs) PF179. Figure 12B: QRT-PCR for miR-106b and miR-17-5p, and their hosts MCM7 and c13orf25, respectively, in early passage (Young) versus late passage (Old) fibroblasts. Data are represented as mean $\pm$ SD.

FIGs. 13A-D are graphs and photographs illustrating the establishment of the IMR90 and CAFs systems. Lung primary human fibroblasts IMR90 and prostate-cancer associated fibroblasts (CAFs) PFCA179 were infected with a retrovirus encoding for either a small hairpin RNA targeting p53 (p53i) or a control RNAi (Con), and grown until the onset of replicative senescence. Figure 13A: A Western blot depicting p53 and p21 downregulation upon the stable expression of the p53 small hairpin RNA. Figure 13B: QRT-PCR analyses of p53 and p21 mRNA levels. Figure 13C: SA- β -Gal staining for late passage IMR90 and CAFs. Figure 13D: QRT-PCR analysis for the non-coding RNA BIC and its resident miRNA miR-155 in WI-38, CAFs and IMR90 cells. Samples were collected from early passage cultures (Young) and from late passage cultures (Old).

FIGs. 14A-B are graphs illustrating that E2F induces miR-106b/93/25. Figure 14A: WI-38 cells were stably infected with ER-E2F1 and treated with 4-OHT. QRT-PCR analyses demonstrated upregulation of a known E2F1 target, Cyclin E, as well as of host mRNAs and miRNAs representatives of the three paralogous polycistrons miR-106b/93/25, miR-17-92 and miR-106a-92. Figure 14B: WI-38 cells were infected with the oncoprotein E1A or a control vector and QRT-PCR revealed upregulation of the genes described above. Data are represented as mean $\pm$ SD.

FIGs. 15A-B are graphs illustrating that miR-106b/93/25 are induced by E2F in cancer cell lines. E2F induces the levels of miR-106b/93/25 polycistron in H1299 lung carcinoma cell line (Figure 15A) and U2OS osteosarcoma cell line (Figure 15B) and treated with 4-OHT for the indicated time periods. QRT-PCR analyses demonstrate upregulation of a known E2F1 target, Cyclin E; as well as of MCM7 and its resident miRNAs.

FIGs. 16A-D are graphs and photographs illustrating that MCM7 and miR-106b are repressed by Nutlin-activated p53 in an E2F-dependent manner. Figures 16A-B: WI-38 were infected with a retrovirus encoding for either a small hairpin RNA targeting p53 (p53i) or a control shRNA (Con) and treated with 10 μ M Nutlin-3 for 24 or 48 hours.

QRT-PCR (Figure 16A) and Western blotting (Figure 16B) analyses demonstrate p53 stabilization that resulted in a robust activation of p21 and repression of E2F1 mRNA and protein levels. MCM7 and its resident miR-106b were repressed in a p53-dependent manner upon Nutlin-3 treatment. Figures 16C-D. WI-38 cells were infected with E1A or a control vector and treated with 10 μ M Nutlin-3 for 24 hours. E1A elevated E2F transactivation activity, resulting in the induction of Cyclin E and E2F1 itself as well as of MCM7 and miR-106b. Nutlin treatment of the control-infected cells repressed transcription of E2F1 and its targets. E1A abolished this repression, indicating that the repression of E2F1 by p53 is necessary for the p53-dependent downregulation of MCM7 and miR-106b. GAPDH protein levels serve as loading controls in Figures 16B and D. QRT-PCR data are represented as mean $\pm$ SD.

FIGs. 17A-D are graphs and photographs illustrating that overexpression of miR-106b/93/25 polycistron results in silencing of cell-cycle related genes. WI-38 primary fibroblasts and MCF10A mammary cells were infected with a retrovirus encoding for either the genomic region that contains miR-106b/93/25 or an empty vector control. Figure 17A: Western blot analysis of reported and novel cell-cycle regulating targets of the overexpressed miRs. Overexpression of miR-106b/93/25 reduced the protein levels of E2F1, pRb, p130, E2F1 and p21 in both cell types and of p57 in WI-38 cells. GAPDH and β -tubulin serve as loading controls. Figure 17B: QRT-PCR analysis of the mRNA levels of the genes presented in (Figure 17A). Values represent the fold change of each mRNA relative to the empty vector infected cells. Figure 17C: Expression pattern of predicted targets of at least five miRs from the '*p53-repressed miR cluster*'. mRNA expression levels are derived from WI-38 cells that underwent immortalization and gradual *in-vitro* transformation (the cell status is indicated below) as described in (Milyavsky *et al*, 2003, Cancer Res 63: 7147-7157). This expression pattern was found to be significantly coherent (EC score=0.14, EC p-value=5x10⁻³). Figure 17D: Promoter analysis performed on the genes from (Figure 17C) (using AMADEUS) revealed enrichment for E2F motif (p-value=2.2x10⁻¹³). Genes with E2F motif in their promoter are indicated in black in the bar on the right.

FIG. 18 is a graphical representation of the miRNAs from the three paralogous polycistrons and their cell-cycle associated targets. Targeting of cell-cycle associated genes by miRNAs that belong to the miR-17-93, miR-106a-93 and miR-106b-25 polycistrons as predicted by PicTar. Black areas indicate predicted targeting.

FIGs. 19A-D are graphs and photographs illustrating that miR-106b/93/25 polycistron promotes proliferation. Overexpression of miR-106b/93/25 polycistron in WI-38 cells promotes proliferation as evident from enhanced growth rate (Figure 19A), increased proportion of S-phase cells (Figure 19B), increased colony formation efficiency (Figure 19C), and decreased SA- β -Gal staining (Figure 19D).

FIG. 20 is a schematic model for the cell-cycle regulatory model comprising E2F, p53, miRs, and other cell-cycle regulators. Arrows correspond to direct transcriptional activation, while bar-headed lines represent direct or indirect inhibition mediated by the following mechanisms: post-transcription gene silencing (miRs and their targets), protein binding and inactivation (pocket proteins and E2F; as well as CDK inhibitors and CDKs, that in turn inhibit pocket proteins by phosphorylation).

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a method of identifying components of a biological pathway. In addition, the present invention relates to use of identified components for regulating diseases associated with altered cell proliferation.

Regulatory RNAs, constitutes a considerable portion of mammalian genomes, and these genes serve as key players in the regulatory network of living cells. Among these regulatory RNAs are the microRNAs, small RNAs that mediate posttranscriptional gene silencing through inhibition of protein production or degradation of mRNAs. So far little is known about the extent of regulation by miRs, and their potential cooperation with other regulatory layers in the network.

The present inventors set out to uncover local and global architectural features of the mammalian miR regulatory network. Using evolutionarily conserved potential binding sites of miRs in human targets, and conserved binding sites of TFs in promoters, two regulation networks were uncovered. The first depicts combinatorial interactions between pairs of miRs with many shared targets. The network reveals several levels of hierarchy, whereby a few miRs interact with many other lowly-connected miR partners (Figure 3A). The present inventors revealed hundreds of “target hubs” genes, many of which are transcription regulators (see Table 1, herein below), each potentially subject to massive regulation by dozens of miRs. The second network which was uncovered by the present inventors consists of miR-TF pairs that coregulate large sets of common targets (see Tables 9-11 herein below). Using bioinformatic analysis and data mining techniques, the

present inventors discovered that the network consists of several recurring motifs. Most notably, in a significant fraction of the miR–TF coregulators the TF appears to regulate the miR, or to be regulated by the miR, forming a diversity of feed forward loops (FFL). Together these findings provide new insights on the architecture of the combined transcriptional–post transcriptional regulatory network.

One of the FFLs that came out of the present analysis is a composite loop in which the TF regulates the miR and the miR appears to regulate the TF. The circuit consists of the transcription factor E2F1 and the miR106b/93/25 polycistron. From this analysis, the present inventors predicted that E2F1 may regulate (and be regulated by) miRs in this cluster.

In order to corroborate the above prediction, the present inventors established isogenic cell cultures that differ in their p53 status and analyzed their miRNA profiles both under normal conditions as well as in contexts that involve p53 activation. The present inventors showed that the miRs of the miR106b/93/25 polycistron and paralogues thereof were part of a set of miRs that were transcriptionally repressed by the tumor suppressor, p53 in primary cells (Figure 11) and that this repression was E2F1-mediated (Figures 14A-B, 15A-B and 16A-D). Whilst further reducing the present invention to practice, the present inventors showed that these microRNAs silence anti-proliferative genes, which themselves are E2F1 targets (Figures 17A-D). Finally, the present inventors showed that similarly to p53 inactivation, overexpression of representative microRNAs promotes proliferation and delays senescence, manifesting the detrimental phenotypic consequence of perturbations in this circuit (Figures 19A-D). Together these findings position microRNAs as novel key players in the context of mammalian cell proliferation regulatory network.

Thus, according to one aspect of the present invention, there is provided a method of identifying components of a biological pathway, the method comprising selecting a transcription factor and a microRNA pair which regulate a common gene, the transcription factor and the microRNA being the components of the biological pathway.

As used herein, the phrase "biological pathway" refers to a discrete cell function or process that is carried out by a gene product (RNA, protein or small molecule metabolite) or a subset of gene products, such as a signaling pathway, a metabolic pathway or a regulatory pathway including pathways involved in cell motility, cell morphology, cellular transformation, cell growth and death and cell communication.

Exemplary biological pathways include anabolic, catabolic, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as cell walls. Biological pathways that are usually required for proliferation of cells or microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, electron transport chains, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

The biological pathway may be in any organism, including but not limited to prokaryotic and eukaryotic organisms (e.g. plants, animals including mammals and yeast).

The phrase "components of a biological pathway", as used herein, refers to at least one transcription factor and one microRNA. It will be appreciated that after elucidation of the transcription factor and microRNA involved in the pathway, the method of this aspect of the present invention may also be used to indirectly uncover other components (including receptors, target genes, signaling molecules, second messenger molecules etc.) belonging to the same pathway, such components being known to interact or be involved with the uncovered transcription factor and microRNA.

As used herein, the phrase "transcription factor" refers to a polypeptide that binds to DNA and regulates gene transcription, and includes regulators that have a positive or a negative effect on transcription initiation or progression.

Information concerning transcription factors (e.g. lists thereof and sequences of transcription factor binding domains) may be found on databases such as for example the protein lounge transcription factor database (www.proteinlounge.com) and the jasper database ([www.jaspar.genereg.net](http://jaspar.genereg.net)).

Target sites in the mRNA being regulated by the transcription factor may be in the 5' UTR or the 3' UTR region.

Exemplary classes of transcription factors are summarized herein below.

1. Superclass: Basic Domains (Basic-helix-loop-helix):

Class: Leucine zipper factors (bZIP) - including Family: AP-1(-like) components; includes (c-Fos/c-Jun), Family: CREB; Family: C/EBP-like factors; Family: bZIP / PAR; Family: Plant G-box binding factors; Family: ZIP only

Class: Helix-loop-helix factors (bHLH) – including Ubiquitous (class A) factors; Myogenic transcription factors (MyoD); Achaete-Scute; Tal/Twist/Atonal/Hen.

Class: Helix-loop-helix / leucine zipper factors (bHLH-ZIP) - including Ubiquitous bHLH-ZIP factors; includes USF (*USF1*, *USF2*); SREBP (SREBP); Family: Cell-cycle controlling factors; includes c-Myc.

Class: NF-1 - including Family: NF-1 (*NF1C*).

5 Class: RF-X - including RF-X (*NFX2*, *NFX3*, *NFX5*).

Class: bHSH.

2 Superclass: Zinc-coordinating DNA-binding domains:

Class: Cys4 zinc finger of nuclear receptor type - including Steroid hormone receptors, Thyroid hormone receptor-like factors

10 Class: diverse Cys4 zinc fingers including GATA-Factors

Class: Cys2His2 zinc finger domain - including Ubiquitous factors, includes TFIIIA, Sp1, Developmental / cell cycle regulators; includes Krüppel, Large factors with NF-6B-like binding properties.

Class: Cys6 cysteine-zinc cluster;

15 Class: Zinc fingers of alternating composition.

3 Superclass: Helix-turn-helix

Class: Homeo domain - including Homeo domain only; includes Ubx; POU domain factors; includes Oct; Homeo domain with LIM region and homeo domain plus zinc finger motifs.

20 Class: Paired box - including Paired plus homeo domain and Paired domain only.

Class: Fork head / winged helix – including Developmental regulators; includes forkhead; Tissue-specific regulators; Cell-cycle controlling factors and other regulators.

Class: Heat Shock Factors – including HSF.

Class: Tryptophan clusters - including Myb, Ets-type, Interferon regulatory factors.

25 Class: TEA domain - including TEA (*TEAD1*, *TEAD2*, *TEAD3*, *TEAD4*).

4 Superclass: beta-Scaffold Factors with Minor Groove Contacts

Class: RHR (Rel homology region) - including Rel/ankyrin; NF-kappaB, ankyrin only and NF-AT (*NFATC1*, *NFATC2*, *NFATC3*).

Class: STAT – including STAT.

30 Class: p53 – including p53.

Class: MADS box – including Regulators of differentiation; includes (Mef2) and Responders to external signals, SRF (serum response factor) (*SRF*).

Class: beta-Barrel alpha-helix transcription factors

Class: TATA binding proteins

Class: Heteromeric CCAAT factors:

Class: Grainyhead

Class: Cold-shock domain factors

Class: Runt

5 0 Superclass: Other Transcription Factors – including: Copper fist proteins: HMGI(Y) (*HMGAI*), HMGI(Y), Pocket domain, E1A-like factors, AP2/EREBP-related factors, AP2, EREBP, AP2/B3, ARF, ABI and RAV.

10 The term "microRNA" as used herein refers to a small RNA transcribed from genes encoding primary transcripts of various sizes. MicroRNAs have been identified in both animals and plants. The primary transcript (termed the "pri-miRNA") is processed through various nucleolytic steps to a shorter precursor miRNA, or "pre-miRNA." The pre-miRNA is present in a folded form so that the final (mature) miRNA is present in a duplex, the two strands being referred to as the miRNA (the strand that will eventually basepair with the target). The pre-miRNA is a substrate for a form of dicer that removes the miRNA duplex from the precursor, after which, similarly to siRNAs, the duplex can be taken into the RNA-induced silencing complex (RISC) complex.

15 The resulting siRNA-like duplex, which may comprise mismatches, comprises the mature miRNA and a similar-sized fragment known as the miRNA*. The miRNA and miRNA* may be derived from opposing arms of the pri-miRNA and pre-miRNA. 20 MiRNA* sequences may be found in libraries of cloned miRNAs but typically at lower frequency than the miRNAs.

25 Although initially present as a double-stranded species with miRNA*, the miRNA eventually becomes incorporated as a single-stranded RNA into the RISC. Various proteins can form the RISC, which can lead to variability in specificity for miRNA/miRNA* duplexes, binding site of the target gene, activity of miRNA (repress or activate), and which strand of the miRNA/miRNA* duplex is loaded in to the RISC.

30 When the miRNA strand of the miRNA:miRNA* duplex is loaded into the RISC, the miRNA* is typically removed and degraded. The strand of the miRNA:miRNA* duplex that is loaded into the RISC may be the strand whose 5' end is less tightly paired. In cases where both ends of the miRNA:miRNA* have roughly equivalent 5' pairing, both miRNA and miRNA* may have gene silencing activity.

 The RISC acts to identify target nucleic acids based on high levels of complementarity between the miRNA and the mRNA, especially by nucleotides 2-8 of the miRNA. A number of studies have looked at the base-pairing requirement between

miRNA and its mRNA target for achieving efficient inhibition of translation (reviewed by Bartel 2004, Cell 116-281). In mammalian cells, the first 8 nucleotides of the miRNA are thought to be important (Doench & Sharp 2004 GenesDev 2004-504). However, other parts of the microRNA may also participate in mRNA binding. Moreover, sufficient base pairing at the 3' can compensate for insufficient pairing at the 5' (Brennecke et al, 2005 PLoS 3-e85). Computation studies, analyzing miRNA binding on whole genomes have suggested a specific role for bases 2-7 at the 5' of the miRNA in target binding but the role of the first nucleotide, found usually to be "A" was also recognized (Lewis et al 2005 Cell 120-15). Similarly, nucleotides 1-7 or 2-8 were used to identify and validate targets by Krek et al (2005, Nat Genet 37-495).

It will be appreciated that multiple miRNAs may regulate the same mRNA target by recognizing the same or multiple sites.

MiRNAs may direct the RISC to downregulate gene expression by either of two mechanisms: mRNA cleavage or translational repression. The miRNA may specify cleavage of the mRNA if the mRNA has a certain degree of complementarity to the miRNA. When a miRNA guides cleavage, the cut may be between the nucleotides pairing to residues 10 and 11 of the miRNA. Alternatively, the miRNA may repress translation if the miRNA does not have the requisite degree of complementarity to the miRNA. Translational repression may be more prevalent in animals since animals may have a lower degree of complementarity between the miRNA and binding site.

Of note, there may be variability in the 5' and 3' ends of any pair of miRNA and miRNA*. This variability may be due to variability in the enzymatic processing of Drosha and Dicer with respect to the site of cleavage. Variability at the 5' and 3' ends of miRNA and miRNA* may also be due to mismatches in the stem structures of the pri-miRNA and pre-miRNA. The mismatches of the stem strands may lead to a population of different hairpin structures. Variability in the stem structures may also lead to variability in the products of cleavage by Drosha and Dicer.

Micro-RNAs can be identified via various databases including for example the micro-RNA registry (www.dotsangerdotacdotuk/Software/Rfam/mirna/index.shtml) and sequences of miRNAs may be obtained from micrornadotsangerdotacdotuk/sequences/. Methods of identifying novel miRNAs are known in the art - see for example Bentwich et al., Nat Genet. 2005 Jul;37(7):766-70. Epub 2005 Jun 19.

As mentioned, the present method is effected by selecting a transcription factor and a microRNA pair which regulate a common gene.

The term "regulate" as used herein refers to either up-regulation or down-regulation.

According to one embodiment of this aspect of the present invention the selection process is effected by analyzing gene sequences and determining if a known or predicted binding site for both a microRNA and a transcription factor is present. For miRNAs, the target sites in a mRNA of a transcribed gene may be in the 5' UTR, the 3' UTR or in the coding region. For TFs, the target sites are generally found upstream of the transcription start sites. Typically, TFs bind to the promoter region of a gene. The length of the gene sequence analyzed is selected such that it is long enough to include all potential targets, yet short enough to eliminate false positives. Accordingly, a typical length of DNA between about 5 kb and 10 kb upstream of the transcription start site (TSS) may be analyzed for transcription factor targets. Putative regulatory regions for miRNAs may be determined as further described in the Examples section below. For example, the sequence that lies about 10 kb upstream of the 5' most pre-miR in each miR cluster may be analyzed.

Various bioinformatic tools are available for analyzing gene sequences and determining if they comprise TF or miRNA binding sites (i.e. targets).

For TFs, tools such as TRANSFAC [Matys V, Fricke E, Geffers R, Gossling E, Haubrock M, et al. (2003) *Nucleic Acids Res* 31: 374–378] version 8.3, defined by the UCSC hg17 genome assembly, in the tfbsConsSites (genomedotucscdotedu/) and tfbsConsFactors may be used.

For miRNAs, tools such as TargetScan [Lewis BP, Burge CB, Bartel DP (2005) *Cell* 120: 15–20; Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB (2003) *Cell* 115: 787–798] (www.targetscan.org) and PicTar [Krek A, Grun D, Poy MN, Wolf R, Rosenberg L, et al. (2005) *Nat Genet* 37: 495–500] (genomedotucscdotedu) may be used.

In order to ensure that false positive assignments of miRs or TFs to targets does not occur, targets may be selected based on evolutionary conservation in at least two species (e.g. human and mouse) or more – see the Examples section herein below.

Other methods may be used to increase the accuracy of results obtained using bioinformatic methods e.g. a noise tolerance analysis as described in the Examples section herein below.

According to one embodiment of this aspect of the present invention the selection process is effected by experimentally determining whether a specific TF or miRNA regulate a specific gene. It will be appreciated that this form of experimentation may be

effected in place of the bioinformatic searches or as a corroboration of a result obtained from a bioinformatic search.

Thus, for example a method of determining whether a specific transcription factor binds to and regulates transcription of a gene may be effected by transfecting a polynucleotide encoding the promoter region of a particular gene linked to a detectable protein (i.e. reporter protein) into a cell – i.e. a reporter based assay. The method further comprises introducing the transcription factor into the cell (e.g. by transfection of an expression vector encoding the agent) and detecting the detectable protein whereby the amount of the detectable protein reflects the transcriptional activity of the promoter. It will be appreciated that the polynucleotide sequence of any protein that may be readily detected may be transcriptionally linked to the promoter. Thus for example, the protein may be a phosphorescent protein such as luciferase, a fluorescent protein such as green fluorescent protein, a chemiluminescent protein or may be a non-directly detectable protein for which an antibody is available for detection thereof. Cells for analyzing transcriptional activity are typically selected to ensure the presence of necessary cofactors and the absence factors which may potentially down-regulate the tested promoter.

A similar assay may be performed for analyzing whether a particular miRNA regulates a gene. Typically a level of reporter polypeptide is measured prior to and following transfection with a polynucleotide encoding the miRNA. A down-regulation of the reporter polypeptide indicates that the miRNA regulates the gene.

Using bioinformatic techniques, the present inventors have uncovered transcription factor and microRNA pairs that regulate common genes. These pairs are listed in Tables 5-8 of the Examples section herein below.

Pairs uncovered according to the teachings of the present invention can be stored as a database on storage devices, preferably in one or more computer-readable media, which contains information for each stored pair.

The information record may comprise, in fields or subfields, information relating to identification of the pair (including an identification code), date of identification of the pair, tools used to uncover the pair, the biological pathway with which it interacts and other potential components of that pathway.

The present inventors have also determined that as well as transcription factors and miRNAs regulating common genes other levels of crosstalk and regulation exist between these two regulatory agents. Thus for example, the present inventors have shown that subset of the pairs listed in Tables 5-8, comprise miRNAs whose gene contains a binding

site for its paired transcription factor (see Figure 4; Tables 9-11 of the Examples section herein below). As another example, the present inventors have shown that a subset of the pairs listed in Tables 5-8, comprise transcription factors whose gene contains a binding site for its paired microRNA (see Figure 4; Table 9-11 of the Examples section herein below).

5 In addition the present inventors have shown that a subset of the pairs listed in Tables 5-8 of the Examples section herein below, comprise transcription factors whose gene comprises a binding site for its paired microRNA and comprise miRNAs whose gene comprises a binding site for its paired transcription factor (see Figure 4; Tables 9-11 of the Examples section herein below). For example, the present inventors have shown that
10 miR-93 comprises an E2F1 binding site and E2F1 comprises a miR-93 binding site and furthermore that miR-93 and E2F1 regulate common genes.

Another level of regulation uncovered by the present inventors is where the transcription factor (of the miRNA/transcription factor pair) regulates a transcription of an additional transcription factor, and the microRNA comprises a binding site for that
15 additional transcription factor. The components involved in this type of regulation are listed in Tables 12-14 of the Examples section herein below.

It will be appreciated that characterization of components of biological pathways and their targets can potentially be utilized to treat diseases associated with such biological pathways.

20 Thus, for example since miR-93 was shown to be regulated by E2F1 and vice versa, this miRNA (including paralogues thereof and other members of its polycistron) may be used to regulate pathways which are known to involve E2F1 (such as cell proliferation and apoptosis, controlling genes regulating S phase entry and DNA synthesis).

In corroboration of the above in silico result, the present inventors have shown that
25 the above identified group of microRNAs silence anti-proliferative genes, (Figures 17A-D) and overexpression thereof promotes cell proliferation (Figures 19A-D).

Thus, according to another aspect of the present invention there is provided a method of treating a hyperproliferative disease in a subject. The method comprises administering to the subject a therapeutically effective amount of a polynucleotide agent
30 capable of down-regulating at least one microRNA selected from the group consisting of miR-106b (SEQ ID NO: 29), miR-93 (SEQ ID NO: 30), miR-25 (SEQ ID NO: 31), miR-17 (SEQ ID NO: 32), miR-18a (SEQ ID NO: 33), miR-19a (SEQ ID NO: 34), miR-20a (SEQ ID NO: 35), miR-19b-1 (SEQ ID NO: 36), miR-92a-1 (SEQ ID NO: 37), miR-106a (SEQ ID NO: 38), miR-18b (SEQ ID NO: 39), miR-20b (SEQ ID NO: 40), miR-19b-2

(SEQ ID NO: 41), miR-92-2* (SEQ ID NO: 42), hsa-miR-19b-1* (SEQ ID NO: 43) miR-15b (SEQ ID NO: 44) and miR-16 (SEQ ID NO: 45) hsa-miR-92a-2* (SEQ ID NO: 46), and hsa-miR-92a-1* (SEQ ID NO: 47) into the subject.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

As used herein, the term "subject" refers to an animal, preferably a mammal, most preferably a human being, including both young and old human beings of both sexes who suffer from or are predisposed to a pathology listed herein below. The subject according to this aspect of the present invention may suffer from a pathology associated with abnormal cell proliferation.

Hyperproliferative conditions that can be treated according to the present invention are, but not limited to, brain, skin (such as melanoma), bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, gynaecological (such as ovarian) or thyroid cancer; other epitheliomas; cysts in various organs; warts and wart-like tumours induced by virus infection; fibrosarcoma and its metastases. In another embodiment, the present invention relates to treatment of non-cancerous hyperproliferative disorder, such as benign hyperplasia of skin or prostate (e.g. benign prostatic hypertrophy), synovial hyperplasia in rheumatoid arthritis, inflammatory bowel disease, restenosis, atherosclerosis, thrombosis, scleroderma or fibrosis.

As used herein the term "cancer" refers to the presence of cells possessing characteristics typical of cancer-causing cells, for example, uncontrolled proliferation, loss of specialized functions, immortality, significant metastatic potential, significant increase in anti-apoptotic activity, rapid growth and proliferation rate, and certain characteristic morphology and cellular markers. In some circumstances, cancer cells will be in the form of a tumor; such cells may exist locally within an animal, or circulate in the blood stream as independent cells, for example, leukemic cells.

Specific examples of cancer which can be treated using the compositions of the present invention include, but are not limited to, adrenocortical carcinoma, hereditary; bladder cancer; breast cancer; breast cancer, ductal; breast cancer, invasive intraductal; breast cancer, sporadic; breast cancer, susceptibility to; breast cancer, type 4; breast cancer, type 4; breast cancer-1; breast cancer-3; breast-ovarian cancer; Burkitt's lymphoma; cervical carcinoma; colorectal adenoma; colorectal cancer; colorectal cancer, hereditary

nonpolyposis, type 1; colorectal cancer, hereditary nonpolyposis, type 2; colorectal cancer, hereditary nonpolyposis, type 3; colorectal cancer, hereditary nonpolyposis, type 6; colorectal cancer, hereditary nonpolyposis, type 7; dermatofibrosarcoma protuberans; endometrial carcinoma; esophageal cancer; gastric cancer, fibrosarcoma, glioblastoma multiforme; glomus tumors, multiple; hepatoblastoma; hepatocellular cancer; hepatocellular carcinoma; leukemia, acute lymphoblastic; leukemia, acute myeloid; leukemia, acute myeloid, with eosinophilia; leukemia, acute nonlymphocytic; leukemia, chronic myeloid; Li-Fraumeni syndrome; liposarcoma, lung cancer; lung cancer, small cell; lymphoma, non-Hodgkin's; lynch cancer family syndrome II; male germ cell tumor; mast cell leukemia; medullary thyroid; medulloblastoma; melanoma, meningioma; multiple endocrine neoplasia; myeloid malignancy, predisposition to; myxosarcoma, neuroblastoma; osteosarcoma; ovarian cancer; ovarian cancer, serous; ovarian carcinoma; ovarian sex cord tumors; pancreatic cancer; pancreatic endocrine tumors; paraganglioma, familial nonchromaffin; pilomatricoma; pituitary tumor, invasive; prostate adenocarcinoma; prostate cancer; renal cell carcinoma, papillary, familial and sporadic; retinoblastoma; rhabdoid predisposition syndrome, familial; rhabdoid tumors; rhabdomyosarcoma; small-cell cancer of lung; soft tissue sarcoma, squamous cell carcinoma, head and neck; T-cell acute lymphoblastic leukemia; Turcot syndrome with glioblastoma; tylosis with esophageal cancer; uterine cervix carcinoma, Wilms' tumor, type 2; and Wilms' tumor, type 1, and the like.

Polynucleotide agents capable of downregulating the miRNAs of the present invention (also referred to herein as anti-miRNAs) typically comprise a sequence that is capable of blocking the activity of a miRNA or miRNA*, such as by binding to the pre-miRNA, pre-miRNA, miRNA or miRNA* (*e.g.* antisense or RNA silencing), or by binding to the target binding site. The sequence of the anti-miRNA may comprise (a) at least 5 nucleotides that are substantially identical or complimentary to the 5' of a miRNA and at least 5-12 nucleotides that are substantially complimentary to the flanking regions of the target site from the 5' end of the miRNA, or (b) at least 5-12 nucleotides that are substantially identical or complimentary to the 3' of a miRNA and at least 5 nucleotide that are substantially complimentary to the flanking region of the target site from the 3' end of the miRNA.

The term "polynucleotide" refers to a single-stranded or double-stranded oligomer or polymer of ribonucleic acid (RNA), deoxyribonucleic acid (DNA) or mimetics thereof. This term includes polynucleotides and/or oligonucleotides derived from naturally

occurring nucleic acids molecules (e.g., RNA or DNA), synthetic polynucleotide and/or oligonucleotide molecules composed of naturally occurring bases, sugars, and covalent internucleoside linkages (e.g., backbone), as well as synthetic polynucleotides and/or oligonucleotides having non-naturally occurring portions, which function similarly to
5 respective naturally occurring portions.

The length of the polynucleotide of the present invention is optionally of 200 nucleotides or less, optionally 175 nucleotides or less, optionally 150 nucleotides or less, optionally 125 nucleotides or less, optionally of 100 nucleotides or less, optionally of 90 nucleotides or less, optionally 80 nucleotides or less, optionally 70 nucleotides or less,
10 optionally 60 nucleotides or less, optionally 50 nucleotides or less, optionally 40 nucleotides or less, optionally 30 nucleotides or less, e.g., 29 nucleotides, 28 nucleotides, 27 nucleotides, 26 nucleotides, 25 nucleotides, 24 nucleotides, 23 nucleotides, 22 nucleotides, 21 nucleotides, 20 nucleotides, 19 nucleotides, 18 nucleotides, 17 nucleotides, 16 nucleotides, 15 nucleotides, optionally between 12 and 24 nucleotides, optionally
15 between 5-15, optionally, between 5-25, or optionally about 20-25 nucleotides.

The polynucleotides (including oligonucleotides) designed according to the teachings of the present invention can be generated according to any oligonucleotide synthesis method known in the art, including both enzymatic syntheses or solid-phase syntheses. Equipment and reagents for executing solid-phase synthesis are commercially
20 available from, for example, Applied Biosystems. Any other means for such synthesis may also be employed; the actual synthesis of the oligonucleotides is well within the capabilities of one skilled in the art and can be accomplished via established methodologies as detailed in, for example: Sambrook, J. and Russell, D. W. (2001), "Molecular Cloning: A Laboratory Manual"; Ausubel, R. M. et al., eds. (1994, 1989),
25 "Current Protocols in Molecular Biology," Volumes I-III, John Wiley & Sons, Baltimore, Maryland; Perbal, B. (1988), "A Practical Guide to Molecular Cloning," John Wiley & Sons, New York; and Gait, M. J., ed. (1984), "Oligonucleotide Synthesis"; utilizing solid-phase chemistry, e.g. cyanoethyl phosphoramidite followed by deprotection, desalting, and purification by, for example, an automated trityl-on method or HPLC.

30 It will be appreciated that a polynucleotide comprising an RNA molecule can be also generated using an expression vector as is further described hereinbelow.

Preferably, the polynucleotide of the present invention is a modified polynucleotide. Polynucleotides can be modified using various methods known in the art.

For example, the oligonucleotides or polynucleotides of the present invention may

comprise heterocyclic nucleosides consisting of purines and the pyrimidines bases, bonded in a 3'-to-5' phosphodiester linkage.

Preferably used oligonucleotides or polynucleotides are those modified either in backbone, internucleoside linkages, or bases, as is broadly described hereinunder.

5 Specific examples of preferred oligonucleotides or polynucleotides useful according to this aspect of the present invention include oligonucleotides or polynucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides or polynucleotides having modified backbones include those that retain a phosphorus atom in the backbone, as disclosed in U.S. Pat. Nos.: 4,469,863; 4,476,301; 10 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050.

Preferred modified oligonucleotide or polynucleotide backbones include, for example: phosphorothioates; chiral phosphorothioates; phosphorodithioates; 15 phosphotriesters; aminoalkyl phosphotriesters; methyl and other alkyl phosphonates, including 3'-alkylene phosphonates and chiral phosphonates; phosphinates; phosphoramidates, including 3'-amino phosphoramidate and aminoalkylphosphoramidates; thionophosphoramidates; thionoalkylphosphonates; thionoalkylphosphotriesters; and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogues of these, and those 20 having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts, and free acid forms of the above modifications can also be used.

Alternatively, modified oligonucleotide or polynucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short-chain alkyl or 25 cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short-chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide, and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and 30 thioformacetyl backbones; alkene-containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts, as disclosed in U.S. Pat. Nos.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677;

5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439.

Other oligonucleotides or polynucleotides which may be used according to the present invention are those modified in both sugar and the internucleoside linkage, *i.e.*, the backbone of the nucleotide units is replaced with novel groups. The base units are maintained for complementation with the appropriate polynucleotide target. An example of such an oligonucleotide mimetic includes a peptide nucleic acid (PNA). A PNA oligonucleotide refers to an oligonucleotide where the sugar-backbone is replaced with an amide-containing backbone, in particular an aminoethylglycine backbone. The bases are retained and are bound directly or indirectly to aza-nitrogen atoms of the amide portion of the backbone. United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262; each of which is herein incorporated by reference. Other backbone modifications which may be used in the present invention are disclosed in U.S. Pat. No. 6,303,374.

Oligonucleotides or polynucleotides of the present invention may also include base modifications or substitutions. As used herein, "unmodified" or "natural" bases include the purine bases adenine (A) and guanine (G) and the pyrimidine bases thymine (T), cytosine (C), and uracil (U). "Modified" bases include but are not limited to other synthetic and natural bases, such as: 5-methylcytosine (5-me-C); 5-hydroxymethyl cytosine; xanthine; hypoxanthine; 2-aminoadenine; 6-methyl and other alkyl derivatives of adenine and guanine; 2-propyl and other alkyl derivatives of adenine and guanine; 2-thiouracil, 2-thiothymine, and 2-thiocytosine; 5-halouracil and cytosine; 5-propynyl uracil and cytosine; 6-azo uracil, cytosine, and thymine; 5-uracil (pseudouracil); 4-thiouracil; 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl, and other 8-substituted adenines and guanines; 5-halo, particularly 5-bromo, 5-trifluoromethyl, and other 5-substituted uracils and cytosines; 7-methylguanine and 7-methyladenine; 8-azaguanine and 8-azaadenine; 7-deazaguanine and 7-deazaadenine; and 3-deazaguanine and 3-deazaadenine. Additional modified bases include those disclosed in: U.S. Pat. No. 3,687,808; Kroschwitz, J. I., ed. (1990), "The Concise Encyclopedia Of Polymer Science And Engineering," pages 858-859, John Wiley & Sons; Englisch et al. (1991), "Angewandte Chemie," International Edition, 30, 613; and Sanghvi, Y. S., "Antisense Research and Applications," Chapter 15, pages 289-302, S. T. Crooke and B. Lebleu, eds., CRC Press, 1993. Such modified bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines, and N-2, N-6, and O-6-substituted

purines, including 2-aminopropyladenine, 5-propynyluracil, and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y. S. et al. (1993), "Antisense Research and Applications," pages 276-278, CRC Press, Boca Raton), and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Polynucleotide agents capable of down-regulating miRNAs are known in the art – see for example Weiler et al., Gene Therapy (2006) 13, 496–502, Davis et al., Nucleic Acids Res. 2006; 34(8): 2294–2304, USPTO Application No: 20070287179.

The present invention also contemplates treating degenerative diseases by administration of the miRNAs of the present invention.

Since as is mentioned hereinabove, micro-RNAs are processed molecules derived from specific precursors (*i.e.*, pre-miRNA), upregulation of a specific miRNA function can be effected using a specific miRNA precursor molecule.

Pre-miR designs exist to all of the known miRNAs listed in the miRNA Registry and can be readily designed for any research.

The phrase "degenerative disease" refers to a disease or disorder resulting from a decrease in cellular proliferation.

Exemplary degenerative diseases neurodegenerative diseases, including but not limited to Parkinson's, Multiple Sclerosis, Huntington's disease, action tremors and tardive dyskinesia, panic, anxiety, depression, alcoholism, insomnia and manic behavior, Alzheimer's, ALS and epilepsy.

It will be appreciated that the subject can be treated *in vivo* (*i.e.*, inside the organism) or *ex vivo* (e.g., in a tissue culture). In case the cells are treated *ex vivo*, the method preferably includes a step of administering such cells back to the individual (*ex vivo* cell therapy). *In vivo* and *ex vivo* therapies are further discussed hereinbelow.

As mentioned hereinabove, the polynucleotides of the present invention (e.g., an RNA molecule such as those set forth by SEQ ID NOs:1-16) can be generated using an expression vector.

To express an exogenous polynucleotide (*i.e.*, to produce an RNA molecule) in mammalian cells, a nucleic acid sequence encoding the polynucleotide of the present invention (e.g., SEQ ID NO:1-16) is typically ligated into a nucleic acid construct suitable for mammalian cell expression. Such a nucleic acid construct includes a promoter sequence for directing transcription of the polynucleotide sequence in the cell in a constitutive or inducible manner.

Constitutive promoters suitable for use with the present invention are promoter sequences which are active under most environmental conditions and most types of cells such as the cytomegalovirus (CMV) and Rous sarcoma virus (RSV). Inducible promoters suitable for use with the present invention include for example the tetracycline-inducible promoter (Zabala M, et al., Cancer Res. 2004, 64(8): 2799-804).

The nucleic acid construct (also referred to herein as an "expression vector") of the present invention includes additional sequences which render this vector suitable for replication and integration in prokaryotes, eukaryotes, or preferably both (e.g., shuttle vectors). In addition, typical cloning vectors may also contain a transcription and translation initiation sequence, transcription and translation terminator and a polyadenylation signal.

Eukaryotic promoters typically contain two types of recognition sequences, the TATA box and upstream promoter elements. The TATA box, located 25-30 base pairs upstream of the transcription initiation site, is thought to be involved in directing RNA polymerase to begin RNA synthesis. The other upstream promoter elements determine the rate at which transcription is initiated.

Preferably, the promoter utilized by the nucleic acid construct of the present invention is active in the specific cell population transformed. Examples of cell type-specific and/or tissue-specific promoters include promoters such as albumin that is liver specific [Pinkert et al., (1987) Genes Dev. 1:268-277], lymphoid specific promoters [Calame et al., (1988) Adv. Immunol. 43:235-275]; in particular promoters of T-cell receptors [Winoto et al., (1989) EMBO J. 8:729-733] and immunoglobulins; [Banerji et al. (1983) Cell 33:729-740], neuron-specific promoters such as the neurofilament promoter [Byrne et al. (1989) Proc. Natl. Acad. Sci. USA 86:5473-5477], pancreas-specific promoters [Edlun et al. (1985) Science 230:912-916] or mammary gland-specific promoters such as the milk whey promoter (U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166).

Enhancer elements can stimulate transcription up to 1,000 fold from linked homologous or heterologous promoters. Enhancers are active when placed downstream or upstream from the transcription initiation site. Many enhancer elements derived from viruses have a broad host range and are active in a variety of tissues. For example, the SV40 early gene enhancer is suitable for many cell types. Other enhancer/promoter combinations that are suitable for the present invention include those derived from polyoma virus, human or murine cytomegalovirus (CMV), the long term repeat from

various retroviruses such as murine leukemia virus, murine or Rous sarcoma virus and HIV. See, *Enhancers and Eukaryotic Expression*, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 1983, which is incorporated herein by reference.

In the construction of the expression vector, the promoter is preferably positioned approximately the same distance from the heterologous transcription start site as it is from the transcription start site in its natural setting. As is known in the art, however, some variation in this distance can be accommodated without loss of promoter function.

Polyadenylation sequences can also be added to the expression vector in order to increase RNA stability [Soreq et al., 1974; J. Mol Biol. 88: 233-45).

Two distinct sequence elements are required for accurate and efficient polyadenylation: GU or U rich sequences located downstream from the polyadenylation site and a highly conserved sequence of six nucleotides, AAUAAA, located 11-30 nucleotides upstream. Termination and polyadenylation signals that are suitable for the present invention include those derived from SV40.

In addition to the elements already described, the expression vector of the present invention may typically contain other specialized elements intended to increase the level of expression of cloned nucleic acids or to facilitate the identification of cells that carry the recombinant DNA. For example, a number of animal viruses contain DNA sequences that promote the extra chromosomal replication of the viral genome in permissive cell types. Plasmids bearing these viral replicons are replicated episomally as long as the appropriate factors are provided by genes either carried on the plasmid or with the genome of the host cell.

The vector may or may not include a eukaryotic replicon. If a eukaryotic replicon is present, then the vector is amplifiable in eukaryotic cells using the appropriate selectable marker. If the vector does not comprise a eukaryotic replicon, no episomal amplification is possible. Instead, the recombinant DNA integrates into the genome of the engineered cell, where the promoter directs expression of the desired nucleic acid.

Examples of mammalian expression vectors include, but are not limited to, pcDNA3, pcDNA3.1(+/-), pGL3, pZeoSV2(+/-), pSecTag2, pDisplay, pEF/myc/cyto, pCMV/myc/cyto, pCR3.1, pSinRep5, DH26S, DHBB, pNMT1, pNMT41, pNMT81, which are available from Invitrogen, pCI which is available from Promega, pMbac, pPbac, pBK-RSV and pBK-CMV which are available from Strategene, pTRES which is available from Clontech, and their derivatives.

Expression vectors containing regulatory elements from eukaryotic viruses such as retroviruses can be also used. SV40 vectors include pSVT7 and pMT2. Vectors derived from bovine papilloma virus include pBV-1MTHA, and vectors derived from Epstein Bar virus include pHEBO, and p2O5. Other exemplary vectors include pMSG, pAV009/A⁺,
5 pMTO10/A⁺, pMAMneo-5, baculovirus pDSVE, and any other vector allowing expression of proteins under the direction of the SV-40 early promoter, SV-40 later promoter, metallothionein promoter, murine mammary tumor virus promoter, Rous sarcoma virus promoter, polyhedrin promoter, or other promoters shown effective for expression in eukaryotic cells.

10 As described above, viruses are very specialized infectious agents that have evolved, in many cases, to elude host defense mechanisms. Typically, viruses infect and propagate in specific cell types. The targeting specificity of viral vectors utilizes its natural specificity to specifically target predetermined cell types and thereby introduce a recombinant gene into the infected cell. Thus, the type of vector used by the present
15 invention will depend on the cell type transformed. The ability to select suitable vectors according to the cell type transformed is well within the capabilities of the ordinary skilled artisan and as such no general description of selection consideration is provided herein. For example, bone marrow cells can be targeted using the human T cell leukemia virus type I (HTLV-I) and kidney cells may be targeted using the heterologous promoter present
20 in the baculovirus Autographa californica nucleopolyhedrovirus (AcMNPV) as described in Liang CY et al., 2004 (Arch Virol. 149: 51-60).

Recombinant viral vectors are useful for *in vivo* expression of the polynucleotide of the present invention since they offer advantages such as lateral infection and targeting specificity. Lateral infection is inherent in the life cycle of, for example, retrovirus and is
25 the process by which a single infected cell produces many progeny virions that bud off and infect neighboring cells. The result is that a large area becomes rapidly infected, most of which was not initially infected by the original viral particles. This is in contrast to vertical-type of infection in which the infectious agent spreads only through daughter progeny. Viral vectors can also be produced that are unable to spread laterally. This
30 characteristic can be useful if the desired purpose is to introduce a specified gene into only a localized number of targeted cells.

Various methods can be used to introduce the expression vector of the present invention into cells. Such methods are generally described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Springs Harbor Laboratory, New York (1989, 1992),

in Ausubel et al., Current Protocols in Molecular Biology, John Wiley and Sons, Baltimore, Md. (1989), Chang et al., Somatic Gene Therapy, CRC Press, Ann Arbor, Mich. (1995), Vega et al., Gene Targeting, CRC Press, Ann Arbor Mich. (1995), Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworths, Boston Mass. (1988) and Gilboa et al. [Biotechniques 4 (6): 504-512, 1986] and include, for example, stable or transient transfection, lipofection, electroporation and infection with recombinant viral vectors. In addition, see U.S. Pat. Nos. 5,464,764 and 5,487,992 for positive-negative selection methods.

Introduction of nucleic acids by viral infection offers several advantages over other methods such as lipofection and electroporation, since higher transfection efficiency can be obtained due to the infectious nature of viruses.

Currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral or non-viral constructs, such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV) and lipid-based systems. Useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol [Tonkinson et al., Cancer Investigation, 14(1): 54-65 (1996)]. The most preferred constructs for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral construct such as a retroviral construct includes at least one transcriptional promoter/enhancer or locus-defining element(s), or other elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used, unless it is already present in the viral construct. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

As mentioned hereinabove, a variety of prokaryotic or eukaryotic cells can be used as host-expression systems to express the polynucleotides of the present invention. These include, but are not limited to, microorganisms, such as bacteria transformed with a recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vector containing the coding sequence; yeast transformed with recombinant yeast expression vectors containing the coding sequence; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors, such as Ti plasmid, containing

the coding sequence. Mammalian expression systems can also be used to express the polynucleotides of the present invention.

Examples of bacterial constructs include the pET series of *E. coli* expression vectors [Studier et al. (1990) *Methods in Enzymol.* 185:60-89].

5 In yeast, a number of vectors containing constitutive or inducible promoters can be used, as disclosed in U.S. Pat. Application No: 5,932,447. Alternatively, vectors can be used which promote integration of foreign DNA sequences into the yeast chromosome.

10 In cases where plant expression vectors are used, the expression of the coding sequence can be driven by a number of promoters. For example, viral promoters such as the 35S RNA and 19S RNA promoters of CaMV [Brisson et al. (1984) *Nature* 310:511-514], or the coat protein promoter to TMV [Takamatsu et al. (1987) *EMBO J.* 6:307-311] can be used. Alternatively, plant promoters such as the small subunit of RUBISCO [Coruzzi et al. (1984) *EMBO J.* 3:1671-1680 and Brogli et al., (1984) *Science* 224:838-843] or heat shock promoters, e.g., soybean hsp17.5-E or hsp17.3-B [Gurley et al. (1986) 15 *Mol. Cell. Biol.* 6:559-565] can be used. These constructs can be introduced into plant cells using Ti plasmid, Ri plasmid, plant viral vectors, direct DNA transformation, microinjection, electroporation and other techniques well known to the skilled artisan. See, for example, Weissbach & Weissbach, 1988, *Methods for Plant Molecular Biology*, Academic Press, NY, Section VIII, pp 421-463.

20 Other expression systems such as insects and mammalian host cell systems which are well known in the art and are further described hereinbelow can also be used by the present invention.

For *ex vivo* therapy, cells are preferably treated with the polynucleotides of the present invention (e.g., anti micro-RNA or microRNA), following which they are 25 administered to the subject (individual) which is in need thereof.

Administration of the *ex vivo* treated cells of the present invention can be effected using any suitable route of introduction, such as intravenous, intraperitoneal, intra-kidney, intra-gastrointestinal track, subcutaneous, transcutaneous, intramuscular, intracutaneous, intrathecal, epidural, and rectal. According to presently preferred embodiments, the *ex vivo* 30 treated cells of the present invention may be introduced to the individual using intravenous, intra-kidney, intra-gastrointestinal track, and/or intraperitoneal administration.

The cells used for *ex vivo* treatment according to the present invention can be derived from either autologous sources, such as self bone marrow cells, or from allogeneic sources, such as bone marrow or other cells derived from non-autologous sources. Since

non-autologous cells are likely to induce an immune reaction when administered to the body, several approaches have been developed to reduce the likelihood of rejection of non-autologous cells. These include either suppressing the recipient immune system or encapsulating the non-autologous cells or tissues in immunoisolating, semipermeable membranes before transplantation.

Encapsulation techniques are generally classified as microencapsulation, involving small spherical vehicles, and macroencapsulation, involving larger flat-sheet and hollow-fiber membranes (Uludag, H. et al. (2000). Technology of mammalian cell encapsulation. *Adv Drug Deliv Rev* 42, 29-64).

Methods of preparing microcapsules are known in the art and include for example those disclosed in: Lu, M. Z. et al. (2000). Cell encapsulation with alginate and alpha-phenoxycinnamylidene-acetylated poly(allylamine). *Biotechnol Bioeng* 70, 479-483; Chang, T. M. and Prakash, S. (2001) Procedures for microencapsulation of enzymes, cells and genetically engineered microorganisms. *Mol Biotechnol* 17, 249-260; and Lu, M. Z., et al. (2000). A novel cell encapsulation method using photosensitive poly(allylamine alpha-cyanocinnamylideneacetate). *J Microencapsul* 17, 245-521.

For example, microcapsules are prepared using modified collagen in a complex with a ter-polymer shell of 2-hydroxyethyl methylacrylate (HEMA), methacrylic acid (MAA), and methyl methacrylate (MMA), resulting in a capsule thickness of 2-5 μm . Such microcapsules can be further encapsulated with an additional 2-5 μm of ter-polymer shells in order to impart a negatively charged smooth surface and to minimize plasma protein absorption (Chia, S. M. et al. (2002). Multi-layered microcapsules for cell encapsulation. *Biomaterials* 23, 849-856).

Other microcapsules are based on alginate, a marine polysaccharide (Sambanis, A. (2003). Encapsulated islets in diabetes treatment. *Diabetes Thechnol Ther* 5, 665-668), or its derivatives. For example, microcapsules can be prepared by the polyelectrolyte complexation between the polyanions sodium alginate and sodium cellulose sulphate and the polycation poly(methylene-co-guanidine) hydrochloride in the presence of calcium chloride.

It will be appreciated that cell encapsulation is improved when smaller capsules are used. Thus, for instance, the quality control, mechanical stability, diffusion properties, and in vitro activities of encapsulated cells improved when the capsule size was reduced from 1 mm to 400 μm (Canaple, L. et al. (2002). Improving cell encapsulation through size

control. *J Biomater Sci Polym Ed* 13, 783-96). Moreover, nanoporous biocapsules with well-controlled pore size as small as 7 nm, tailored surface chemistries, and precise microarchitectures were found to successfully immunoisolate microenvironments for cells (See: Williams, D. (1999). Small is beautiful: microparticle and nanoparticle technology in medical devices. *Med Device Technol* 10, 6-9; and Desai, T. A. (2002). Microfabrication technology for pancreatic cell encapsulation. *Expert Opin Biol Ther* 2, 633-646).

The polynucleotides and/or the expression vectors of the present invention can be administered to the individual per se or as part of a pharmaceutical composition where it is mixed with suitable carriers or excipients.

As used herein, a "pharmaceutical composition" refers to a preparation of one or more of the active ingredients described herein with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

As used herein, the term "active ingredient" refers to the agent, the polynucleotide and/or the expression vector of the present invention accountable for the intended biological effect.

Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier," which may be used interchangeably, refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. An adjuvant is included under these phrases.

Herein, the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Techniques for formulation and administration of drugs may be found in the latest edition of "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, which is herein fully incorporated by reference.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, especially transnasal, intestinal, or parenteral delivery, including intramuscular, subcutaneous, and intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intracardiac, intranasal, or intraocular injections.

Alternately, one may administer the pharmaceutical composition in a local rather than systemic manner, for example, via injection of the pharmaceutical composition directly into a tissue region of a patient.

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the active ingredients of the pharmaceutical composition may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological salt buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the pharmaceutical composition to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries as desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, and sodium carbomethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate, may be added.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, and

suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions that can be used orally include push-fit capsules
5 made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid
10 polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by nasal inhalation, the active ingredients for use according to
15 the present invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, or carbon dioxide. In the case of a pressurized aerosol, the dosage may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example,
20 gelatin for use in a dispenser may be formulated containing a powder mix of the compound and a suitable powder base, such as lactose or starch.

The pharmaceutical composition described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with,
25 optionally, an added preservative. The compositions may be suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the
30 active ingredients may be prepared as appropriate oily or water-based injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters such as ethyl oleate, triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension

may also contain suitable stabilizers or agents that increase the solubility of the active ingredients, to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., a sterile, pyrogen-free, water-based solution, before use.

5 The pharmaceutical composition of the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, using, for example, conventional suppository bases such as cocoa butter or other glycerides.

Pharmaceutical compositions suitable for use in the context of the present invention include compositions wherein the active ingredients are contained in an amount effective
10 to achieve the intended purpose. More specifically, a "therapeutically effective amount" means an amount of active ingredients (e.g., the agent, the polynucleotide and/or the expression vector of the present invention) effective to prevent, alleviate, or ameliorate symptoms of the pathology [e.g., a pathology related to increased or decreased cell proliferation such as cancer or prolong the survival of the subject being treated.

15 Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any preparation used in the methods of the invention, the dosage or the therapeutically effective amount can be estimated initially from in vitro and cell culture assays. For example, a dose can be formulated in animal models to achieve a desired
20 concentration or titer. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the active ingredients described herein can be determined by standard pharmaceutical procedures in vitro, in cell cultures or experimental animals. The data obtained from these in vitro and cell culture assays and animal studies
25 can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. (See, e.g., Fingl, E. et al. (1975), "The Pharmacological Basis of Therapeutics," Ch. 1, p.1.)

30 Dosage amount and administration intervals may be adjusted individually to provide sufficient plasma or brain levels of the active ingredient to induce or suppress the biological effect (*i.e.*, minimally effective concentration, MEC). The MEC will vary for each preparation, but can be estimated from in vitro data. Dosages necessary to achieve

the MEC will depend on individual characteristics and route of administration. Detection assays can be used to determine plasma concentrations.

Depending on the severity and responsiveness of the condition to be treated, dosing can be of a single or a plurality of administrations, with course of treatment lasting from several days to several weeks, or until cure is effected or diminution of the disease state is achieved.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

Compositions of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA-approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser device may also be accompanied by a notice in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may include labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation of the invention formulated in a pharmaceutically acceptable carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as further detailed above.

It is expected that during the life of a patent maturing from this application many novel miRNAs will be developed and the scope of the term miRNA is intended to include all such new technologies *a priori*.

As used herein the term "about" refers to $\pm 10\%$

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

Reference is now made to the following examples, which together with the above
5 descriptions, illustrate the invention in a non limiting fashion.

Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current
10 Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (eds) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold
15 Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., ed. (1994); "Culture of Animal Cells - A Manual of Basic Technique" by Freshney, Wiley-Liss, N. Y. (1994), Third Edition; "Current Protocols in Immunology" Volumes I-III Coligan J. E., ed. (1994); Stites et al.
20 (eds), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (eds), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533;
25 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., ed. (1984); "Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., eds. (1984); "Animal Cell Culture" Freshney, R. I., ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984)
30 and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, CA (1990); Marshak et al., "Strategies for Protein Purification and Characterization - A Laboratory Course Manual" CSHL Press (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein

are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

EXAMPLE 1

Connectivity Distributions in the miR-Gene Network

Materials and Methods

MiRs and their predicted targets: miRs and their predicted targets were taken from two previously published studies: TargetScan [Lewis BP, et al., (2005) Cell 120: 15–20; Lewis BP, et al., (2003) Cell 115: 787–798] (www.dottargets.candotorg) and PicTar [Krek A, et al. (2005) Nat Genet 37: 495–500] (genomedotucscdotedu). Both resources predict and assign target genes to miRs based on evolutionary conservation between human, mouse, rat and dog. TargetScan targets were downloaded and gene symbols were converted to RefSeq IDs using UCSC mysql databases. PicTar targets were downloaded from the UCSC hg17 database where they are presented as the picTarMiRNA4Way track.

Target hubs analysis: Target hubs were defined as genes which are targeted by more miRs than the 99th percentile of the maximal value in 100 randomizations of the columns in the miR to gene assignment matrix, each preserved the total number of targets per miR. According to this procedure, in the TargetScan dataset, target hubs were defined as genes which are targeted by more than 15 miRs (there were 470 such genes), and in the PicTar dataset, target hubs were defined as genes targeted by more than 20 miRs (834 genes). For original and randomized distributions see Figure 1A.

To check whether the target hubs contain many miR target sites merely because they have, on average, longer 3' UTRs, the length of 3' UTRs for all RefSeq genes was retrieved from UCSC hg17. A randomization test was performed on this 3' UTR length data, in which sets of genes were randomly picked from the data with distribution of 3' UTR length that was as similar as possible (see below) to that of the target hubs. For each such set of genes the average number of different miRs predicted to target them was calculated. This randomization procedure was repeated 100 times, and the distribution of average number of miRs was derived (Figures 6A-B). The figure shows that these values are significantly lower than the average of the original target hubs, indicating that the length is neither necessary nor sufficient for a gene to be a target hub.

100 random sets of genes were generated with length distributions similar to that of the target hubs by the following procedure. For each target hub with UTR length, L_{TH} , a set of genes with similar UTR length was defined, which included all the genes in the dataset

with a UTR length equal to L_{TH} , or longer up to an additional 5 % of L_{TH} (genes which did not have such sets were excluded from the analysis). Then, a representative from each set to be included in the randomized version of target hubs was randomly selected. miR density in genes 3' UTRs was calculated as the number of miRs targeting a gene divided by its 3' UTR length. 3' UTR length was extracted from the UCSC database.

When defining high density target hubs, the density cutoffs were selected to be the top 85th percentile of the entire distribution of densities. Of note, this distribution included only genes that participated in the present analyses and thus does not contain genes with a density of zero (i.e., zero predicted sites in the UTR).

Degree-preserving matrix randomization: To determine a p -value on the co-occurrence rate of a pair of two miRs, a co-occurrence score was first defined. The Meet/Min score was selected [Goldberg DS, Roth FP (2003) Proc Natl Acad Sci U S A 100: 4372–4376; Ravasz E, et al., (2002) Science 297: 1551–1555], which is formulated in the main text, and it was calculated on the matrix of miR to target genes. For the purpose of p -value calculations, a null model of randomized matrices was defined, which preserves the matrix statistics such that for each gene the number of miRs targeting it, and for each miR the number of genes it targets remains the same as in the original data. This model was first introduced as a randomization model for networks [Shen-Orr SS, et al., (2002) Nat Genet 31: 64–68], which preserved all in- and out-degrees in a given network, and thereby controlling for the possibility that significance of a phenomenon may be merely attributed to the degree distribution in the network. Randomized matrices were created by the edge-swapping procedure, starting from the original matrix of miR to target gene predictions. Two pairs of miR and target gene were randomly picked, miR_{i1} - $gene_{j1}$ and miR_{i2} - $gene_{j2}$, and, after verifying that miR_{i1} does not already target $gene_{j2}$ and miR_{i2} does not already target $gene_{j1}$, the switch of an edge in the matrix was performed, so that after the swap there is a “0” instead of “1” in the positions $i_{1,j1}$ and $i_{2,j2}$ in the matrix, and a “1” instead of a “0” in the positions $i_{1,j2}$ and $i_{2,j1}$ in the matrix. To decide how many swapping events were needed before the matrix was “well randomized,” the number of edges that were actually swapped were monitored and compared with the number of changed edges in a randomly shuffled matrix. This number was followed during the swapping steps and it was realized that it plateaued at about 100,000 steps. Thus in all subsequent analyses the swapping procedure was repeated for 100,000 steps.

During the calculation of the Meet/Min score for a pair of miRs in the original data, genes that contained a match to the two miRs were excluded if the two sites physically overlapped on the target's 3' UTR. In addition, the present inventors filtered out from the analysis, pairs of miRs whose seeds were identical (overlap of seven out of seven nucleotides, positions 2–8 of the miR). These two precautions were taken to eliminate the possibility of overestimating the significance of the rate of miR co-occurrence due to seed sequence similarity between different miRs.

After having calculated the co-occurrence p -values and avoidance p -values for all possible miR pairs, the present inventors controlled for multiple hypotheses using FDR and only pairs that passed FDR of 0.05 were considered to be significantly co-occurring or avoiding.

Significant miR–TF co-occurring pairs: For the task of identifying miR–TF pairs that significantly co-occur in a high number of target genes, a p -value was calculated (using a cumulative hypergeometric test) on each pair of regulators as was performed before for pairs of TFs [Pilpel Y, et al., (2001) Nat Genet 29: 153–159]. The hypergeometric p -value was calculated after the RefSeq genes were mapped to a unique set of Gene IDs, to reduce redundancy in the set. In the miR–TF p -value calculations, the total number of genes in the hypergeometric analysis was calculated as the number of genes that appeared (i.e., had at least one binding site) in both datasets. Genes that appeared only in the TF dataset or in the miR dataset were excluded and were not counted. FDR was used to correct for multiple hypotheses testing, and the set of significant pairs of coregulators was determined.

Co-occurrence p -values were also calculated for all possible miR–TF pairs using the new randomization method presented above. Specifically, both the matrix which assigns TFs to genes and the matrix with assignments of miRs to genes were subjected to 100,000 iterations of the edge-swapping procedure. In total 1,000 such pairs of randomized matrices were generated. The co-occurrence p -value of a given TF–miR pair is the fraction of the randomized matrix pairs in which this pair's Meet/Min score was higher than the pair's Meet/Min score in the original matrices, and the corresponding z -score is the difference between the original Meet/Min score and the mean of the score in the randomized matrices, divided by their standard deviation.

Most reassuringly, when checking the overlap of these significant pairs with the significant pairs that passed FDR cutoff of 0.3 using the hypergeometric model, it was noticed that the overlap was very high; it was more than 72 % for PicTar and 92 % for

TargetScan. For subsequent analyses of network motifs (FFLs and indirect FFL search), all the pairs that passed FDR of 0.3 in the hypergeometric test in the three datasets (see Transcription Factor binding sites section below), and that passed FDR of 0.3 (p -value $< 6 \times 10^{-3}$) in the PicTar 10 kb set, and minimal p -value ($< 10^{-3}$) in the PicTar 5 kb and TargetScan sets were selected, as these already had an extremely high overlap ($> 93\%$) in the hypergeometric derived set.

The final set of significant pairs in the miR–TF network is presented in FDR q -value cutoffs of 0.1, 0.2, and 0.3. With q -value, of 0.1, 20 TF–miR pairs were obtained with significant p -value using the TargetScan dataset, and 267 using the PicTar 10 kb dataset, and 70 using the PicTar 5 kb dataset. With a q -value of 0.2, 60 TF–miR pairs were obtained with significant p -value using the TargetScan dataset, and 555 using the PicTar 10 kb dataset, and 261 using the PicTar 5 kb dataset. With 0.3 104 TF–miR pairs were obtained with significant p -value using the TargetScan dataset, and 916 using the PicTar 10 kb dataset, and 497 using the PicTar 5 kb dataset.

miRs clusters and regulatory regions: As was shown in the past [Tanzer A, Stadler PF (2004) J Mol Biol 339: 327–335], miRs may be clustered on the genome, and are often transcribed as one unit. Therefore, to predict regulatory regions of miRs (i.e., proximal as well as potentially more distant promoters or enhancers) miRs first had to be clustered on the human genome. All 461 pre-miRs in miRBase (micrornadotsangerdotacdotuk) were mapped onto the human genome and clustered according to physical proximity (genomic locations of miRs were taken from UCSC hg17 and some miRs were mapped from hg18 back to hg17 using the UCSC “lift genome” web service). Two pre-miRs, that are consecutive on the genome, were considered belonging to the same cluster if the distance between them was shorter than a cutoff, provided that they are transcribed from the same strand. miRs kept being added to clusters until the first distance that was larger than the cutoff was hit. To learn a meaningful cutoff from the data, the distribution of distances between all neighboring pre-miRs in the genome was plotted. Interestingly, the distribution was found to be bimodal — distances below and above 10 kb (on a log scale, Figure 6A) were highly represented in contrast to a lower representation about 10 kb. This indicated that a reasonable cutoff on the distance between two adjacent miRs that still belong to the same cluster may be 10 kb. Using this clustering procedure, 301 clusters were generated, the majority of which (~82.39 %) consisted of a single miR; the cluster with the highest number of miRs contains 43 miRs (see Figure 7 for the distribution of number of miRs per cluster). In a previous study, which was based on 207 miRs (compared with the 461 used

here), miRs were clustered using different a cutoff [Altuvia Y, et al, (2005) Nucleic Acids Res 33: 2697–2706]. When the cluster analysis was repeated with the current set of miRs, with the previous cutoff, a similar clustering was obtained — 94 % of the present clusters are identical to the clusters generated with the alternative cutoff and average cluster lengths are very similar (unpublished data).

Reassuringly, using expression data of miRs across tissues it was found that miRs that belong to the same cluster have a significant tendency to be coexpressed compared with miRs that do not map to shared clusters (Figure 8B). This tendency is preserved even in cases where miRs that belong to the same cluster are relatively far from each other on the genome (Figure 8B, inset).

The present inventors then defined, as a putative regulatory region of miRs, the sequence that lies 10 kb upstream of the 5' most pre-miR in each miR cluster. The 10 kb promoter length was determined from the data as follows. A distribution of number of conserved TFBS upstream of clusters was generated (Figure 8C). It was found that the number of conserved TFBS gradually declined as a function of the distance from the putative 5' end of the cluster, with a plateau obtained at about 10 kb upstream. The distribution was rather noisy, probably due to the fact that primary-miR transcripts are much longer than the precursor miR that were related to (e.g., the primary transcript of the miR-17-92 cluster is C13orf25, which is 6,795 bp long), and thus the transcription start site (TSS) taken here is only crudely defined. The presence of a TFBS in a miR promoter was considered only if such occurrence was conserved in mouse and rat, as taken from the UCSC hg17 conserved track in the relevant regions.

Transcription factor binding sites: Predicted binding sites for all human mouse and rat PSSMs from TRANSFAC [Matys V, et al. (2003) Nucleic Acids Res 31: 374–378] version 8.3 were used, as they are defined by the UCSC hg17 genome assembly, in the tfbsConsSites (genomedotucsdotedu/) and tfbsConsFactors. All RefSeq genes genomic locations were taken from hg17. To determine the length of upstream regulatory regions, the number of conserved TFBS upstream RefSeq genes as a function of distance from TSS was measured (see Figure 9). The result shows that the signal decays and plateaus between 5 kb and 10 kb upstream of the TSS. The present inventors hence chose to work with two alternative cutoffs of promoter length, 5 kb and 10 kb. The regulatory regions thus defined probably consist of proximal promoters as well as distant enhancers. The recent Affymetrix promoter chip for detection of ChIP experiments with TF binding in human promoters also consists of probes that span 10 kb of regulatory regions, and future

experiments with this chip and as many TFs as possible will allow a better delineation of regulatory regions boundaries. Although regulatory regions which were longer than the common definition were used, use of evolutionary conservation filter gives confidence in the present regulatory region definitions.

5 ***Feed forward loop statistics:*** FFL TF→miR: For all the significant pairs of coregulators (i.e., TF–miR partners that co-occur in a significantly high number of targets) the present inventors investigated whether the TF has a binding site in the putative promoter of the miR cluster from which the miR partner is transcribed. In some cases in which the mature miR sequence is transcribed from more than one genomic locus, all possible regulatory regions of the relevant miR clusters were examined. In addition, each PSSM may belong to a family of PSSMs, with similar binding sites, representing the same TF (a family was defined as several PSSMs representing the same TF, as determined from the UCSC hg17 tfbsConsFactors track). Thus, PSSM–miR pairs are treated as TF–miR pair, and given a pair of PSSM–miR partners, it may be said that the PSSM’s TF regulates the miR if at least one of the PSSMs that corresponds to that TF has a match in the regulatory region of the miR partner (the same procedure was carried out in the randomizations described below).

For testing the FFL miR→TF configuration, the present inventors had to connect first between TRANSFAC PSSMs and the genes encoding the TFs that bind these PSSMs. For that, PSSMs were mapped to the TF they represent which in turn was mapped to a SwissProt ID, these two mappings were done using the UCSC hg17 tfbsConsFactors track. These SwissProt IDs were then mapped to RefSeq IDs, for which the data on miR targets was maintained. This information served also in the process of indirect FFL search; for each of the TF–miR partners, the present inventors checked whether the miR is regulated by another mediator TF, which in turn is regulated by the partner TF. It was noted that not all TFs had a corresponding SwissProt ID in the UCSC hg17 tfbsConsFactors track, and therefore not all pairs served as candidates for the FFL miR→TF and the indirect FFL; only in 74 of the 104 (71 %) TargetScan significant pairs, and in 680 of 916 (74 %) of the PicTar pairs the PSSM could be mapped to a RefSeq gene.

30 The following procedure was used for the calculation of the significance of the FFLs and indirect FFL in the PicTar and TargetScan miR-TF networks. Since there were 104 and 916 pairs of miR-TF partners in the two respective networks, the present inventors have drawn 10,000 times the same number of random pairs of TFs and miRs out of all the possible pairs in each network. The number of each FFL and indirect FFL was recorded in

each randomization and a p -value (and a corresponding z -score) on the hypothesis that a given network motif is over-represented in the network was taken to be the number of random sets with a greater or equal number of motifs in it.

miR and mRNA tissue expression data: The expression profiles of 150 miRs across five healthy human tissues and organs (brain, liver, thymus, testes, and placenta) were previously measured using miR-dedicated microarrays [Barad O, et al. (2004) Genome Res 14: 2486–2494]. miRs from the chips were mapped to PicTar and TargetScan, they cover 154 and 87 of the miRs in the two respective datasets. In addition, data was used from Su AI, et al. (2004) Proc Natl Acad Sci U S A 101: 6062–6067 for human mRNAs expression across the same set of tissues. Both sets of expression data were column centered (chip-wise centering: each chip's values were divided by the chip mean to account for differences in chip intensities) and then log2 transformed. Regarding mRNA expression chips, the present inventors particularly focused on genes coding for the TFs that participated in the present analysis. Using the above mapping of PSSMs to their corresponding TF genes, a total of 127 TFs were identified that could be matched to at least one probe set in the mRNA expression dataset [Su AI, et al. (2004) Proc Natl Acad Sci U S A 101: 6062–6067]. The tissue expression correlation of all significantly co-occurring miR and TF pairs was examined for which there was an expression profile. When more than one gene was attributed to the same TF, the present inventors chose for each pair of TF and miR the one with the highest absolute value of correlation coefficient out of all options. This was consistently done both for the background statistics of all possible TF–miR pairs and for the predicted TF–miR partners. In total, correlation coefficients for 361 such TF–miR partners out of 916 partners in PicTar, and for 30 out of 104 partners in TargetScan were calculated. The miR expression data [Barad O, 2004, Genome Res 14: 2486–2494] consisted of five healthy tissues, and HeLa cells, while the mRNA study that was focused on [Su AI, et al. (2004) Proc Natl Acad Sci U S A 101: 6062–6067] overlapped with the miR data only in the five tissues. Therefore when expression between miRs and TFs was compared, only the five healthy tissues were used, and when expression of miR pairs was compared, all six samples were used.

Noise-tolerance analysis: The assignments of miRs to targets are known to be of limited accuracy. The present inventors thus wanted to assess the noise tolerance of the present results. A procedure previously utilized for the case of network motifs in the bacterial transcription network was adopted [Shen-Orr SS, (2002) Nat Genet 31: 64–68]. The present inventors experimented with different percentages of the connections in the

network that were randomly removed or added and the significance of the present FFL motifs was assessed for each case. Similarly to the findings in the *E. coli* network, it was found that up to 20 %–30 % of the edges can be added or removed without appreciable effect on the FFL significance.

RESULTS

Two datasets of miRs and their predicted target genes were used: TargetScan [Lewis BP, et al., (2005) Cell 120: 15–20; Lewis BP, (2003) Cell 115: 787–798] and PicTar [Krek A, et al. (2005) Nat Genet 37: 495–500]. The miRs used in this analysis are characterized by being evolutionarily conserved and, in addition, their targets were defined based on conservation in orthologous genes in four species (human, mouse, rat and dog). This evolutionary conservation criterion was assumed to constitute a good filter for false positive assignments of miRs to genes. Altogether, 8,672 and 9,152 human (RefSeq) genes were analyzed in the TargetScan and PicTar datasets, respectively, that have at least one predicted miR binding site in their 3' UTR, and a total of 138 miRs and 178 miRs in the respective datasets.

A matrix was constructed whose rows are genes and columns are miRs, in which the ij^{th} element is “1” if gene *i* contains a predicted binding site for miR *j* in its 3' UTR, and “0” otherwise. One such matrix was created for each of the two miR target prediction datasets. For the sake of clarity, from here on “a miR targets a gene” and “a gene contains in its 3' UTR a predicted binding site for a miR” are used interchangeably. First, the matrix was characterized by the distribution of degree connectivity of each gene and of each miR. Figure 1A shows the distribution of the number of miRs assigned per gene, while Figure 1B shows the distribution of number of genes assigned to each miR. Each distribution was compared to a set of distributions, each derived by randomization of the original matrix according to two alternative null models. Along with the distribution of number of miRs per gene (Figure 1A) 100 distributions were plotted, obtained after randomizing each of the columns in the matrix. In this randomization, the number of genes per miR was preserved, yet assigned genes at random to each miR. The distributions obtained after the randomization differed markedly from the original distribution, both in terms of width and shape. While in the randomized distributions genes rarely have binding sites for more than ten different miRs in their 3' UTR, in the original distribution there are hundreds of genes subjected to extensive predicted miR regulation. In Figure 1B the distribution of number of genes per miR is also shown. Along with it is shown a set of distributions obtained by randomizing each of the rows in the matrix, namely by randomly

assigning miRs to each gene, preserving the original number of miRs predicted to target each gene, as in the original matrix. Here, too, the randomized distributions differed from the original one both in shape and width; the original data contains multiple miRs which appear to target more than 400 genes, significantly higher than the number that would be
5 obtained by merely preserving the statistics of number of miR sites in genes UTRs. These observations lead the present inventors to highlight some special properties that seem to be unique to the miR regulatory network.

The distribution of number of miRs regulating each target gene (Figure 1A) has a long right tail in contrast to the distributions in the randomized matrices that looked
10 Gaussian (as befits a sum of independent random variables). The present inventors thus focused on the genes in that tail of the distribution (which are targeted by more than 15 miRs and 20 miRs in the TargetScan and PicTar datasets, respectively, see Materials and Methods for further details and cut-off justification). These genes were named target hubs. There are 470 such genes in the TargetScan dataset. Similar observations were made with
15 the PicTar dataset and identified 834 target hubs — the set of target hubs based on the TargetScan dataset has an 81 % overlap with the target hubs defined by PicTar dataset.

Inspecting the target hubs genes' annotations (using Gene Ontology, GO), it was found that they are highly enriched for developmental processes, specifically for muscle development and nervous system development, as well as for TFs and transcription
20 regulators (see Table 1 herein below).

Table 1

GO Annotation	Target Hubs with High Number of miR Binding Sites		High Density Target Hubs	
	Enrichment p-Value	Number of Target Hubs with Annotation	Enrichment p-Value	Number of Target Hubs with Annotation
Development	4.09E-07	48	3.74E-04	81
DNA Binding	8.59E-09	61	1.31E-04	102
Muscle Development	3.50E-05	8	NS	
Negative Regulation of Transcription, DNA-Dependent	8.12E-05	8	NS	
Nervous System Development	2.34E-10	25	4.39E-04	27
Nucleus	4.80E-06	83	4.07E-05	171
Protein Binding	3.39E-06	94	6.90E-06	200
Regulation of Transcription	1.49E-06	58	1.24E-06	117
Regulation of Transcription from RNA Polymerase II Promoter	4.30E-03	9	2.04E-07	25
Regulation of Transcription, DNA-Dependent	3.13E-07	57	1.69E-07	114
RNA Polymerase II TF Activity	2.26E-06	13	2.36E-10	27
System Development	2.77E-10	25	4.96E-04	27
Transcription	2.38E-06	59	9.78E-07	121
Transcription Coactivator Activity	1.15E-02	6	7.57E-07	18
Transcription Cofactor Activity	3.60E-03	9	1.62E-06	23
TF Activity	7.02E-09	37	1.37E-05	57
TF Binding	2.32E-03	11	1.67E-05	25
Transcription from RNA Polymerase II Promoter	2.88E-08	22	6.20E-09	38
Transcription Regulator Activity	1.82E-09	47	4.34E-08	83
Transcriptional Activator Activity	1.93E-03	9	1.57E-05	20

Table 1. TargetScan Target Hubs GO Functional Enrichment

Target hubs were defined by two alternative definitions: target hubs with high number of miR binding site (more than 15 in the case of TargetScan and more than 20 in the case of PicTar), or as high density target hubs (genes with high density of miRs in their 3' UTRs). The standard method of hypergeometric *p*-value was used to test for functionally enriched GO annotations in each gene set. The results were corrected for multiple hypotheses and annotations were considered significantly enriched if they passed FDR of 0.05. The table presents the union of significant annotations for the high density target hubs and the high miR number target hubs.

Among the transcription regulators in the set of target hubs are included RUNX1, E2F-3, N-MYC, and SP3. Another very intriguing fact is that the *Ago1* gene, one of the

key components of the human RISC (RNAi induced silencing complex), is also a target hub, as in the dataset it appears to be potentially regulated by multiple miRs.

It was suspected, however, that the fact that target hubs host many miR binding sites may result from potentially longer 3' UTRs. Although it was found that target hubs have a distribution of 3' UTR lengths that is significantly longer than that of the rest of the genes in the current analysis (p -value = 4×10^{-85} and p -value = 3×10^{-101} for TargetScan and PicTar target hubs, respectively, using the Kolmogorov-Smirnov test), that many of them have relatively short 3' UTRs. To test whether the high number of miR binding sites in the target hubs is a simple reflection of their 3' UTR lengths a randomization test was performed, in which the present inventors sampled 100 times random gene sets from the entire dataset with the same or very similar length distributions as that of the target hubs (see Materials and Methods). It was found that such gene sets always have a significantly lower average number of miR sites per gene compared with the target hubs. The density of different miRs in the 3' UTRs was further calculated. Density was defined as number of different miRs targeting a gene divided by 3' UTR length. Remarkably it was found that the miR binding site density in the target hubs is significantly higher than in the rest of the genes in the dataset (p -value = 2×10^{-85} and p -value = 6×10^{-124} for the TargetScan and PicTar target hubs, respectively, using the Kolmogorov-Smirnov test; the means are 2.84 and 1.80 times higher in the TargetScan and PicTar dataset means, respectively, see Figures 2A-B). It was concluded that target hubs are rich in binding sites for different miRs to an extent that cannot be explained solely by their 3' UTRs lengths.

Realizing that density of miR binding sites may be an important property by itself, an alternative definition for target hubs was also used — genes with particularly high density of miRs in their 3' UTRs. Genes in the top 85th percentile of the miR binding site density spectrum were collected, and a similar GO enrichment analysis was performed to see whether particular functionalities were enriched among the genes with a high density of miRs. Reassuringly, most of the functionalities that were enriched among the set of target hubs defined by number of different miRs were also significant in the set of high density target hubs (see Table 1). Moreover, it was found that genes that were target hubs according to only one of the two definitions (i.e., genes that are not in the overlap of the two sets) were still significantly enriched for functionalities such as transcription regulator activity and development (unpublished data).

Combinatorial interactions are a fundamental property of the transcription networks. It may be anticipated that, similarly to TFs, miRs may work in combinations.

One way to predict pairs of coregulating miRs is to ask which pairs show a high rate of co-occurrence in the same target genes' 3' UTRs. A common statistical test in the field, previously used in the context of promoter motifs and TF binding site, is the cumulative hypergeometric statistic. According to this model, given the rate of occurrence of each of the regulators alone, and the total number of genes in the analysis, a *p*-value is computed on the size of the set of genes that are shared between the two regulators. The main assumption of this model, that assignment of a gene to the first regulator is independent of the assignment to the second one, is likely fulfilled in the context of fixed-length promoters. Yet when it comes to 3' UTRs of varying length, the assumption does not hold anymore. Some genes, e.g., those with long 3' UTRs, have a higher chance to contain predicted binding sites for miRs, hence a *p*-value calculated based on the hypergeometric model may overestimate the significance of the co-occurrence rate.

Thus, an alternative, randomization-based test for identifying significantly co-occurring miR pairs was devised. The model was designed such that it will capture the underlying distributions in Figures 1 A and B, and test whether a given pair of miRs co-occurs at a higher rate, considering the above distributions as a background. For each pair of miRs, *i* and *j*, with their set of targets, Targets(*i*) and Targets(*j*) respectively, the "Meet/Min" score was calculated [Goldberg DS, Roth FP (2003) Proc Natl Acad Sci U S A 100: 4372–4376; Ravasz E, et al., (2002) Science 297: 1551–1555] defined in the present case as:

$$\frac{|\text{Targets}(i) \cap \text{Targets}(j)|}{\min(|\text{Targets}(i)|, |\text{Targets}(j)|)}$$

namely, the size of the set of genes that contain sites for the two miRs together, divided by the smaller of the two sets of targets (the present inventors filtered from the calculation for each *i, j* pair, 3' UTRs in which the sites for *i* and *j* are physically overlapping to avoid overestimation of significance of miR pairs with an overlapping or similar seed, see Materials and Methods for details). Yet this score is not a statistic, i.e., it lacks an estimate of the probability to obtain such score (or better) by chance given an appropriate null model. Following previous works [Shen-Orr SS, Milo R, Mangan S, Alon U (2002) Nat Genet 31: 64–68] a null model that preserves for each gene the number miRs assigned to it was used, and for each miR the number of genes assigned to it in the input data. The present inventors generated 1,000 randomized matrices according to this null model. In each such matrix the original matrix was randomized in 100,000 steps, using an edge-

swapping algorithm [Shen-Orr SS, Milo R, Mangan S, Alon U (2002) Nat Genet 31: 64–68]. For each such randomized matrix the Meet/Min score for all pairs of miRs was recomputed. The co-occurrence p -value for a pair of miRs was computed according to the pair's Meet/Min score and the population of 1,000 Meet/Min scores obtained for that same pair in each of the 1,000 edge-swapped matrices. The p -value for the pair is defined as the fraction of the 1,000 randomized matrices in which the Meet/Min score of that pair is greater than or equal to the Meet/Min score of the pair in the original matrix.

In addition to calculating a score of co-occurrence, using the same formalism, a score was also calculated that captures the tendency of every two miRs to avoid residing within shared 3' UTRs. A pair of miRs that co-occur in the original matrix significantly less frequently than in the edge-swapped matrices was regarded as avoiding each other. Given the Meet/Min score of co-occurrence for a pair of miRs, and the Meet/Min scores obtained for that pair in the 1,000 edge-swapped matrices, the fraction of randomized scores that were lower than or equal to that obtained in the original matrix for that pair, was calculated as the avoidance p -value of a miR pair.

In both cases of co-occurrence and avoidance, false discovery rate (FDR) was used to control for the testing of multiple hypotheses. In the case of co-occurring miR pairs, using a restrictive FDR threshold (q -value = 0.05), 107 pairs were obtained with significant a p -value in the TargetScan dataset, and 199 pairs in the PicTar dataset (interestingly, the ratio between the number of interactions in the two datasets (~ 0.54) is very close to the ratio expected based on the square of relative number of miRs in each dataset (~ 0.6)). A combinatorial network was created based on the significant co-occurring miR pairs. The top miR pairs are given in Table 2 and are also depicted in Figure 3A.

Table 2

<i>First miR</i>	<i>Number of Targets</i>	<i>Second miR</i>	<i>Number of Targets</i>	<i>Number of Common Genes</i>	<i>Meet/Min Score</i>	<i>Co-Occurrence p-Value</i>
miR-133	317	miR-423	9	4	0.44	<10E-3
miR-147	8	miR-219	210	3	0.38	<10E-3
miR-146	103	miR-423	9	3	0.33	<10E-3
miR-30	737	miR-365	129	41	0.32	<10E-3
miR-362	94	miR-495	503	29	0.31	<10E-3
miR-23	514	miR-362	94	28	0.30	<10E-3
miR-185	135	miR-20	608	40	0.30	<10E-3
miR-181	578	miR-362	94	27	0.29	<10E-3
miR-29	567	miR-362	94	26	0.28	<10E-3
miR-221	211	miR-495	503	58	0.27	<10E-3
miR-25	474	miR-342	126	34	0.27	<10E-3
miR-200b	500	miR-382	88	23	0.26	<10E-3
miR-186	419	miR-362	94	24	0.26	<10E-3
miR-362	94	miR-93	369	24	0.26	<10E-3
miR-362	94	miR-369-3p	361	23	0.24	<10E-3
miR-129	197	miR-381	547	47	0.24	<10E-3
miR-218	454	miR-409-5p	93	22	0.24	<10E-3
miR-19	563	miR-329	182	43	0.24	<10E-3
miR-369-3p	361	miR-495	503	85	0.24	<10E-3

Table 2 above depicts the number of targets each miR has in the specific database, and the number of targets which contain sites for both miRs. Note that in each pairing, genes were filtered out where binding sites for the two miRs physically overlapped, so this *p*-value is not biased by miRs with highly similar seeds. For this reason, the number of target genes may be slightly different for the same miR in two different pairings.

The full list of significant pairs is provided in Table 3 herein below (Full list of TargetScan co-occurring miR pairs that passed FDR of 0.05) and Table 4 herein below (Full list of PicTar co-occurring miR pairs that passed FDR of 0.05).

Table 3

<i>miR1</i>	<i>#targets</i>	<i>miR2</i>	<i>#targets</i>	<i>#common genes</i>	<i>Meet/Min score</i>	<i>co-occurrence pv</i>	<i>seed similarity</i>
miR-133	317	miR-423	9	4	0.44	0	1
miR-147	8	miR-219	210	3	0.38	0	1
miR-146	103	miR-423	9	3	0.33	0	0
miR-30	737	miR-365	129	41	0.32	0	1
miR-362	94	miR-495	503	29	0.31	0	0
miR-23	514	miR-362	94	28	0.30	0	0
miR-185	135	miR-20	608	40	0.30	0	1
miR-181	578	miR-362	94	27	0.29	0	1
miR-29	567	miR-362	94	26	0.28	0	1
miR-221	211	miR-495	503	58	0.27	0	0
miR-25	474	miR-342	126	34	0.27	0	1
miR-200b	500	miR-382	88	23	0.26	0	0
miR-186	419	miR-362	94	24	0.26	0	2
miR-362	94	miR-93	369	24	0.26	0	0
miR-362	94	miR-369-3p	361	23	0.24	0	0
miR-129	197	miR-381	547	47	0.24	0	0
miR-218	454	miR-409-5p	93	22	0.24	0	0
miR-19	563	miR-329	182	43	0.24	0	1
miR-369-3p	361	miR-495	503	85	0.24	0	0
miR-221	211	miR-362	94	22	0.23	0	2
miR-362	94	miR-505	238	22	0.23	0	0
miR-217	160	miR-381	547	37	0.23	0	2
miR-15	567	miR-505	238	55	0.23	0	0
miR-101	445	miR-208	148	34	0.23	0	0
miR-186	419	miR-505	238	54	0.23	0	1
miR-181	576	miR-495	501	113	0.23	0	2
miR-23	514	miR-329	182	41	0.23	0	0
miR-101	443	miR-485-3p	156	35	0.22	0	3
miR-190	85	miR-448	357	19	0.22	0	1
miR-329	182	miR-362	94	21	0.22	0	0
miR-330	373	miR-362	94	21	0.22	0	1
miR-19	563	miR-221	211	47	0.22	0	0
miR-183	245	miR-200b	500	54	0.22	0	0
miR-181	578	miR-93	369	81	0.22	0	1
miR-144	429	miR-208	147	32	0.22	0	1
miR-136	113	miR-210	14	3	0.21	0	1
miR-186	419	miR-329	182	39	0.21	0	0
miR-210	14	miR-335	135	3	0.21	0	0
miR-221	211	miR-369-3p	361	45	0.21	0	2
miR-200b	500	miR-381	547	106	0.21	0	0
miR-18	124	miR-93	369	26	0.21	0	0
miR-129	196	miR-218	453	41	0.21	0	2
miR-101	445	miR-19	563	93	0.21	0	1
miR-329	182	miR-369-3p	360	38	0.21	0	2
miR-185	135	miR-93	369	28	0.21	0	1
miR-369-3p	361	miR-450	126	26	0.21	0	0
miR-214	311	miR-324-3p	146	30	0.21	0	1
miR-144	429	miR-19	563	88	0.21	0	1
miR-221	211	miR-320	408	43	0.20	0	1

miR-330	369	miR-495	499	75	0.20	0	1
miR-129	197	miR-186	419	40	0.20	0	1
miR-205	242	miR-324-5p	84	17	0.20	0	2
miR-362	94	miR-503	235	19	0.20	0	0
miR-101	445	miR-505	238	48	0.20	0	2
miR-320	408	miR-505	238	48	0.20	0	0
miR-144	428	miR-381	545	85	0.20	0	2
miR-153	362	miR-7	254	50	0.20	0	1
miR-186	419	miR-495	503	82	0.20	0	0
miR-134	88	miR-539	319	17	0.19	0	1
miR-185	135	miR-330	373	26	0.19	0	0
miR-377	229	miR-410	381	44	0.19	0	1
miR-204	252	miR-218	454	48	0.19	0	1
miR-144	428	miR-505	237	45	0.19	0	2
miR-133	317	miR-135	379	60	0.19	0	1
miR-101	445	miR-495	503	84	0.19	0	2
miR-130	414	miR-376	133	25	0.19	0	1
miR-448	357	miR-7	254	47	0.19	0	0
miR-183	245	miR-218	454	45	0.18	0	0
miR-342	109	miR-377	214	20	0.18	0	6
miR-382	88	miR-505	238	16	0.18	0	1
miR-320	408	miR-93	369	67	0.18	0	0
miR-185	135	miR-362	94	17	0.18	0	1
miR-135	378	miR-153	362	65	0.18	0	1
miR-185	135	miR-503	235	24	0.18	0	1
miR-101	445	miR-26	509	78	0.18	0	1
miR-186	419	miR-320	408	71	0.17	0	0
miR-135	378	miR-448	357	62	0.17	0	2
miR-135	379	miR-7	254	43	0.17	0	0
miR-186	419	miR-330	373	63	0.17	0	1
miR-134	89	miR-183	245	15	0.17	0	0
miR-329	182	miR-505	238	30	0.16	0	4
miR-205	242	miR-409-5p	93	15	0.16	0	2
miR-129	197	miR-382	88	14	0.16	0	1
miR-190	83	miR-194	214	13	0.16	0	2
miR-132	230	miR-145	340	36	0.16	0	2
miR-185	135	miR-505	238	21	0.16	0	0
miR-221	210	miR-329	181	27	0.15	0	0
miR-503	235	miR-505	238	33	0.14	0	0
miR-33	184	miR-382	87	12	0.14	0	1
miR-221	211	miR-505	238	29	0.14	0	1
miR-33	185	miR-342	126	17	0.13	0	0
miR-136	113	miR-33	185	15	0.13	0	1
miR-324-3p	146	miR-383	91	12	0.13	0	0
miR-33	185	miR-376	133	17	0.13	0	0
miR-151	55	miR-339	121	7	0.13	0	1
miR-28	95	miR-370	184	12	0.13	0	0
miR-185	135	miR-329	182	17	0.13	0	1
miR-329	182	miR-503	235	22	0.12	0	0
miR-193	116	miR-324-3p	146	14	0.12	0	1
miR-34b	224	miR-376	133	16	0.12	0	1
miR-329	182	miR-450	126	15	0.12	0	0

miR-409-5p	93	miR-485-3p	158	11	0.12	0	0
miR-18	124	miR-375	151	14	0.11	0	0
miR-134	89	miR-324-3p	146	10	0.11	0	0
miR-134	89	miR-342	126	10	0.11	0	0
miR-134	89	miR-346	69	7	0.10	0	1
miR-134	89	miR-216	116	8	0.09	0	0

Table 4

miR1	#targets	miR2	#targets	#common genes	Meet/Min score	co-occurrence pv
hsa-miR-106b	532	hsa-miR-93	430	270	0.627907	0
hsa-miR-20a	517	hsa-miR-93	406	240	0.591133	0
hsa-miR-106b	553	hsa-miR-372	277	157	0.566787	0
hsa-miR-107	410	hsa-miR-15b	473	213	0.519512	0
hsa-miR-20a	541	hsa-miR-372	264	133	0.503788	0
hsa-miR-17-5p	418	hsa-miR-93	454	209	0.5	0
hsa-miR-20b	400	hsa-miR-93	452	194	0.485	0
hsa-miR-128a	334	hsa-miR-27b	599	155	0.464072	0
hsa-miR-107	404	hsa-miR-15a	439	187	0.462871	0
hsa-miR-17-5p	446	hsa-miR-372	309	143	0.462783	0
hsa-miR-139	267	hsa-miR-340	11	5	0.454545	0
hsa-miR-33	290	hsa-miR-340	11	5	0.454545	0
hsa-miR-20b	425	hsa-miR-372	313	142	0.453674	0
hsa-miR-107	470	hsa-miR-195	411	185	0.450122	0
hsa-miR-128b	313	hsa-miR-27b	605	140	0.447284	0
hsa-miR-106b	639	hsa-miR-302c	298	133	0.446309	0
hsa-miR-103	295	hsa-miR-15a	465	127	0.430508	0
hsa-miR-128a	393	hsa-miR-27a	526	169	0.430025	0
hsa-miR-20a	639	hsa-miR-302c	281	119	0.423488	0
hsa-miR-106b	637	hsa-miR-302d	309	130	0.420712	0
hsa-miR-130b	446	hsa-miR-152	212	89	0.419811	0
hsa-miR-103	273	hsa-miR-15b	485	114	0.417582	0
hsa-miR-130a	516	hsa-miR-152	143	59	0.412587	0
hsa-miR-103	401	hsa-miR-195	441	165	0.411471	0
hsa-miR-106b	641	hsa-miR-302b	270	110	0.407407	0
hsa-miR-107	425	hsa-miR-16	364	144	0.395604	0
hsa-miR-128b	334	hsa-miR-27a	526	132	0.39521	0
hsa-miR-144	320	hsa-miR-199a-star	238	91	0.382353	0
hsa-miR-101	182	hsa-miR-144	367	69	0.379121	0
hsa-miR-20a	638	hsa-miR-302d	288	108	0.375	0
hsa-miR-106b	637	hsa-miR-302a	282	105	0.37234	0
hsa-miR-103	339	hsa-miR-16	390	125	0.368732	0
hsa-miR-130b	466	hsa-miR-148a	150	55	0.366667	0
hsa-miR-217	196	hsa-miR-340	11	4	0.363636	0

hsa-miR-17-5p	601	hsa-miR-302d	320	116	0.3625	0
hsa-miR-130a	541	hsa-miR-148a	126	45	0.357143	0
hsa-miR-20a	640	hsa-miR-302b	255	91	0.356863	0
hsa-miR-17-5p	607	hsa-miR-302b	280	99	0.353571	0
hsa-miR-182	305	hsa-miR-96	401	107	0.35082	0
hsa-miR-190	100	hsa-miR-30a-5p	753	35	0.35	0
hsa-miR-190	100	hsa-miR-30b	752	35	0.35	0
hsa-miR-190	100	hsa-miR-30c	752	35	0.35	0
hsa-miR-190	100	hsa-miR-30d	754	35	0.35	0
hsa-miR-190	100	hsa-miR-30e-5p	758	35	0.35	0
hsa-let-7e	607	hsa-miR-196a	138	48	0.347826	0
hsa-miR-17-5p	600	hsa-miR-302c	302	104	0.344371	0
hsa-let-7i	620	hsa-miR-196a	129	44	0.341085	0
hsa-let-7c	605	hsa-miR-196a	139	47	0.338129	0
hsa-miR-101	186	hsa-miR-199a-star	324	61	0.327957	0
hsa-miR-20a	640	hsa-miR-302a	264	86	0.325758	0
hsa-miR-196a	137	hsa-miR-98	577	44	0.321168	0
hsa-miR-151	38	hsa-miR-23a	474	12	0.315789	0
hsa-miR-151	38	hsa-miR-23b	478	12	0.315789	0
hsa-let-7b	625	hsa-miR-196a	131	41	0.312977	0
hsa-let-7i	620	hsa-miR-196b	120	37	0.308333	0
hsa-miR-20b	594	hsa-miR-302c	285	87	0.305263	0
hsa-miR-20b	587	hsa-miR-302d	299	91	0.304348	0
hsa-miR-200b	513	hsa-miR-208	66	20	0.30303	0
hsa-miR-20b	595	hsa-miR-302b	258	78	0.302326	0
hsa-let-7a	586	hsa-miR-196a	135	40	0.296296	0
hsa-let-7b	627	hsa-miR-196b	122	36	0.295082	0
hsa-miR-34b	207	hsa-miR-34c	271	61	0.294686	0
hsa-miR-320	431	hsa-miR-9-star	319	94	0.294671	0
hsa-let-7g	602	hsa-miR-196a	129	38	0.294574	0
hsa-miR-130a	560	hsa-miR-19a	527	154	0.29222	0
hsa-let-7a	590	hsa-miR-196b	127	37	0.291339	0
hsa-miR-144	481	hsa-miR-208	66	19	0.287879	0
hsa-let-7e	607	hsa-miR-196b	123	35	0.284553	0

hsa-miR-128a	603	hsa-miR-215	88	25	0.284091	0
hsa-miR-128b	598	hsa-miR-215	88	25	0.284091	0
hsa-miR-20b	588	hsa-miR-302a	282	79	0.280142	0
hsa-miR-196b	126	hsa-miR-98	578	35	0.277778	0
hsa-miR-17-5p	595	hsa-miR-302a	283	78	0.275618	0
hsa-miR-130a	561	hsa-miR-19b	512	141	0.275391	0
hsa-let-7f	582	hsa-miR-196a	131	36	0.274809	0
hsa-miR-130b	464	hsa-miR-148b	114	31	0.27193	0
hsa-let-7d	490	hsa-miR-196a	133	36	0.270677	0
hsa-miR-106b	665	hsa-miR-142-5p	319	86	0.269592	0
hsa-let-7g	602	hsa-miR-196b	120	32	0.266667	0
hsa-miR-19a	539	hsa-miR-301	453	120	0.264901	0
hsa-miR-222	243	hsa-miR-372	667	64	0.263374	0
hsa-miR-142-5p	318	hsa-miR-20a	663	83	0.261006	0
hsa-let-7f	584	hsa-miR-196b	123	32	0.260163	0
hsa-miR-130b	506	hsa-miR-19a	527	131	0.258893	0
hsa-miR-205	288	hsa-miR-324-5p	51	13	0.254902	0
hsa-miR-324-3p	164	hsa-miR-371	20	5	0.25	0
hsa-miR-148a	157	hsa-miR-301	381	39	0.248408	0
hsa-miR-103	679	hsa-miR-199b	226	56	0.247788	0
hsa-miR-199b	226	hsa-miR-19a	620	56	0.247788	0
hsa-miR-199b	226	hsa-miR-19b	616	56	0.247788	0
hsa-miR-19a	620	hsa-miR-222	243	60	0.246914	0
hsa-miR-130b	507	hsa-miR-19b	513	125	0.246548	0
hsa-miR-34a	391	hsa-miR-34b	266	65	0.244361	0
hsa-miR-19b	616	hsa-miR-222	243	59	0.242798	0
hsa-miR-20a	682	hsa-miR-222	243	59	0.242798	0
hsa-miR-152	381	hsa-miR-324-5p	50	12	0.24	0
hsa-miR-181a	548	hsa-miR-217	196	47	0.239796	0
hsa-miR-181b	548	hsa-miR-217	196	47	0.239796	0
hsa-miR-181c	547	hsa-miR-217	196	47	0.239796	0
hsa-miR-144	472	hsa-miR-27b	689	111	0.235169	0
hsa-miR-26b	553	hsa-miR-375	180	42	0.233333	0
hsa-miR-32	504	hsa-miR-342	159	37	0.232704	0
hsa-miR-19b	616	hsa-miR-221	254	59	0.232283	0
hsa-miR-218	486	hsa-miR-222	242	56	0.231405	0
hsa-miR-26a	545	hsa-miR-375	180	41	0.227778	0
hsa-miR-181a	545	hsa-miR-222	239	54	0.225941	0
hsa-miR-181c	544	hsa-miR-222	239	54	0.225941	0
hsa-miR-181a	548	hsa-miR-199b	226	51	0.225664	0
hsa-miR-181c	547	hsa-miR-199b	226	51	0.225664	0
hsa-miR-130a	572	hsa-miR-33	287	64	0.222997	0

hsa-miR-222	234	hsa-miR-320	446	52	0.222222	0
hsa-miR-181b	548	hsa-miR-302a	405	89	0.219753	0
hsa-miR-153	405	hsa-miR-222	243	53	0.218107	0
hsa-miR-181a	548	hsa-miR-302a	405	88	0.217284	0
hsa-miR-181c	547	hsa-miR-302a	405	88	0.217284	0
hsa-miR-106b	681	hsa-miR-19a	603	131	0.217247	0
hsa-miR-152	364	hsa-miR-19a	593	79	0.217033	0
hsa-miR-19b	509	hsa-miR-301	443	96	0.216704	0
hsa-miR-221	245	hsa-miR-320	447	53	0.216327	0
hsa-miR-181b	548	hsa-miR-302d	408	88	0.215686	0
hsa-miR-152	364	hsa-miR-19b	591	78	0.214286	0
hsa-miR-23b	435	hsa-miR-323	258	55	0.213178	0
hsa-miR-218	486	hsa-miR-221	254	54	0.212598	0
hsa-miR-19a	608	hsa-miR-302d	405	86	0.212346	0
hsa-miR-181b	546	hsa-miR-221	250	53	0.212	0
hsa-miR-186	496	hsa-miR-9-star	343	72	0.209913	0
hsa-miR-199b	224	hsa-miR-218	485	47	0.209821	0
hsa-miR-217	196	hsa-miR-320	450	41	0.209184	0
hsa-miR-193b	187	hsa-miR-320	450	39	0.208556	0
hsa-miR-101	479	hsa-miR-19a	620	99	0.206681	0
hsa-miR-101	479	hsa-miR-19b	616	99	0.206681	0
hsa-miR-181a	548	hsa-miR-9-star	344	71	0.206395	0
hsa-miR-181b	548	hsa-miR-9-star	344	71	0.206395	0
hsa-miR-181c	547	hsa-miR-9-star	344	71	0.206395	0
hsa-miR-153	405	hsa-miR-221	254	52	0.204724	0
hsa-miR-126-star	318	hsa-miR-186	496	65	0.204403	0
hsa-miR-144	481	hsa-miR-19b	616	98	0.203742	0
hsa-miR-222	231	hsa-miR-9-star	336	47	0.203463	0
hsa-miR-193b	187	hsa-miR-302a	405	38	0.203209	0
hsa-miR-193b	187	hsa-miR-302d	408	38	0.203209	0
hsa-miR-221	243	hsa-miR-9-star	336	49	0.201646	0
hsa-miR-23a	431	hsa-miR-323	258	52	0.20155	0
hsa-miR-25	351	hsa-miR-342	159	32	0.201258	0
hsa-miR-190	100	hsa-miR-22	313	20	0.2	0
hsa-miR-222	242	hsa-miR-302a	404	48	0.198347	0
hsa-miR-199a-star	475	hsa-miR-19b	616	94	0.197895	0
hsa-miR-186	496	hsa-miR-369-3p	369	73	0.197832	0
hsa-miR-222	243	hsa-miR-302d	408	48	0.197531	0
hsa-miR-10a	148	hsa-miR-367	387	29	0.195946	0
hsa-miR-18b	154	hsa-miR-	405	30	0.194805	0

		302a				
hsa-miR-18b	154	hsa-miR-302d	408	30	0.194805	0
hsa-miR-153	405	hsa-miR-7	293	57	0.194539	0
hsa-miR-222	243	hsa-miR-369-3p	369	47	0.193416	0
hsa-miR-221	254	hsa-miR-369-3p	369	49	0.192913	0
hsa-miR-193b	187	hsa-miR-302c	373	36	0.192513	0
hsa-miR-193a	192	hsa-miR-302d	408	36	0.1875	0
hsa-miR-185	312	hsa-miR-193b	187	35	0.187166	0
hsa-miR-199b	226	hsa-miR-369-3p	369	42	0.185841	0
hsa-miR-221	253	hsa-miR-302a	404	46	0.181818	0
hsa-miR-101	479	hsa-miR-32	503	87	0.181628	0
hsa-miR-221	254	hsa-miR-302d	408	46	0.181102	0
hsa-miR-222	242	hsa-miR-302c	373	43	0.177686	0
hsa-miR-193a	192	hsa-miR-302c	373	34	0.177083	0
hsa-miR-193b	187	hsa-miR-302b	372	33	0.176471	0
hsa-miR-126-star	318	hsa-miR-199a	185	32	0.172973	0
hsa-miR-199a	185	hsa-miR-302c	373	32	0.172973	0
hsa-miR-199a	185	hsa-miR-369-3p	369	32	0.172973	0
hsa-miR-194	222	hsa-miR-302c-star	406	38	0.171171	0
hsa-miR-18b	154	hsa-miR-302c	373	26	0.168831	0
hsa-miR-126-star	316	hsa-miR-369-3p	369	53	0.167722	0
hsa-miR-133a	370	hsa-miR-135b	398	62	0.167568	0
hsa-miR-152	369	hsa-miR-33	287	48	0.167247	0
hsa-miR-185	312	hsa-miR-193a	192	32	0.166667	0
hsa-miR-302d	408	hsa-miR-9-star	344	57	0.165698	0
hsa-miR-133a	370	hsa-miR-135a	394	61	0.164865	0
hsa-miR-185	312	hsa-miR-222	243	40	0.164609	0
hsa-miR-302a	405	hsa-miR-9-star	344	56	0.162791	0
hsa-miR-369-3p	369	hsa-miR-9-star	344	56	0.162791	0
hsa-miR-133b	388	hsa-miR-135b	398	62	0.159794	0
hsa-miR-126-star	318	hsa-miR-199b	226	36	0.159292	0
hsa-miR-133b	388	hsa-miR-	394	61	0.157216	0

		135a				
hsa-miR-302c	373	hsa-miR-9-star	344	54	0.156977	0
hsa-miR-185	312	hsa-miR-221	254	39	0.153543	0
hsa-miR-126-star	318	hsa-miR-222	241	37	0.153527	0
hsa-miR-194	224	hsa-miR-368	126	19	0.150794	0
hsa-miR-139	267	hsa-miR-194	224	33	0.147321	0
hsa-miR-193a	192	hsa-miR-222	243	26	0.135417	0
hsa-miR-193b	187	hsa-miR-222	243	25	0.13369	0
hsa-miR-199b	226	hsa-miR-222	243	30	0.132743	0
hsa-miR-328	236	hsa-miR-331	235	29	0.123404	0
hsa-miR-18b	154	hsa-miR-375	184	19	0.123377	0
hsa-miR-136	138	hsa-miR-375	184	17	0.123188	0
hsa-miR-193a	191	hsa-miR-199a	185	21	0.113514	0
hsa-miR-127	19	hsa-miR-213	9	1	0.111111	0
hsa-miR-193b	186	hsa-miR-199a	185	20	0.108108	0
hsa-miR-191	30	hsa-miR-210	19	2	0.105263	0
hsa-miR-10b	148	hsa-miR-368	126	13	0.103175	0
hsa-miR-134	100	hsa-miR-346	101	10	0.1	0
hsa-miR-134	100	hsa-miR-146a	119	9	0.09	0

This combinatorial network consists of several levels of hierarchy. At the top (Figure 3A) are a handful of miRs which interact with a relatively large number of miR partners, while at the bottom are “end-nodes” with very few miR partners each.

- 5 Examination of the degree distribution in the miR combinatorial network revealed a power-law with slope of about -1.5 and $R^2 = \sim 0.89$ in TargetScan and $R^2 = 0.94$ in PicTar (Figures 3B-C), indicating that the network of coregulating miRs is scale-free (alternative FDR cut-offs also resulted in scale free networks with R^2 always bigger than 0.72). Interestingly, expression data of the miRs provides some support for the predicted
- 10 regulatory interactions between them. It was found that coexpressed miRs tended to have relatively high co-occurrence scores, and significant co-occurrence p -values, while miR pairs with negatively correlated expression tended to avoid residing in shared 3' UTRs (see below).

EXAMPLE 2***Coordinated Regulation of Target Genes by miRs and TFs***

A potential regulatory design in the gene expression network is that genes belonging to the same regulon will be coregulated not only at the transcriptional level, but also posttranscriptionally. One potential realization of this design may be that a particular miR and a particular TF would regulate common targets. A simple means to identify some of the cases of regulatory cooperation between a miR and a TF may be to find TF-miR pairs that co-occur in a large set of shared targets compared to the size expected by chance. Similar to the case of miRs sites in 3' UTRs, the present inventors considered a TF to be present in a human gene's promoter only if its occurrence in the promoter is conserved in the promoters of orthologous genes from mouse and rat (as taken from UCSC, see Materials and Methods). A matrix was then created whose rows are the genes and columns are TFs, with a "1" for the i-th gene and the j-th TF if the TF binding site (TFBS) occurs in the gene's promoter and "0" otherwise.

To identify pairs of TFs and miRs that cooperate in regulating shared target genes the present inventors looked for TF-miR pairs with a high rate of co-occurrence in the promoters and 3' UTRs of the regulated genes. The co-occurrence was tested in shared genes of each of the 409 position specific scoring matrices (PSSMs) representing TF binding sites in TRANSFAC [Matys V, et al. (2003) Nucleic Acids Res 31: 374-37] with each of the 138 and 178 miRs in the TargetScan and PicTar databases respectively. A PSSM and a miR are said to co-occur in the same gene if the PSSM has a conserved binding site in the promoter of the gene and the miR has a conserved predicted site in the gene's 3' UTR. Two statistical models were used to calculate the significance of rate of TF-miR co-occurrence, and ultimately considered TF-miR pairs that were found to be significant according to both tests. First, a hypergeometric *p*-value was calculated based on the number of genes that contain a TFBS in their promoter, the number of genes that contain a miR site in their 3' UTR, and the number of genes that contain both the TF and the miR sites (see Materials and Methods for details). Such *p*-values were computed on all TF-miR pairs and a threshold was set on the *p*-values obtained to account for the multiplicity of hypotheses, using FDR. Using an FDR *q*-value of 0.3, 111 miR-TF pairs were obtained with significant *p*-values using the TargetScan dataset and 1,263 miR-TF pairs with significant *p*-values using the PicTar dataset (see Materials and Methods for number of pairs with more stringent *q*-values). Reassuringly there is a high overlap between the TargetScan and PicTar networks (68.7 % of the TargetScan miR-TF network

pairs were also found to be significant pairs in the PicTar network). The hypergeometric p -value has the advantage of being an analytical model with essentially unlimited resolution. Also, unlike the above situation of miR co-occurring pairs, which exhibited inherent dependency between the two regulators, the present case of TF-miR interaction does not present such limitation. Nevertheless, it was decided to also backup the hypergeometric-based predictions with a randomization test, very similar to the one presented above for the case of miR co-occurrence, that preserves the distribution of number of regulators of each gene, the number of targets of each TF, and the number of targets of each miR in the input datasets. The co-occurrence rates and p -values of all TF-miR pairs Matys V, Fricke E, Geffers R, Gossling E, Haubrock M, et al. (2003) TRANSFAC: transcriptional regulation, from patterns to profiles. Nucleic Acids Res 31: 374-37, and FDR was used as above to account for the multiplicity of hypotheses (see Materials and Methods for details). Reassuringly, 93% and 72% of the hypergeometric-based TF-miR interactions from the TargetScan and PicTar datasets, respectively, were also supported by this alternative model. The rest of the analyses were based on TF-miR pairs that passed the two statistical tests using FDR; there were 104 pairs in the TargetScan dataset and 916 pairs in the PicTar dataset. For simplicity, a TF and a miR that significantly co-occur are termed "partners". Table 5 herein below lists the top TF-miR partners in the TargetScan and PicTar Networks.

Table 5

Dataset	miR	Number of Target Genes	TF	Number of Target Genes	Intersection Size	Hypergeometric Co-Occurrence p-Value	Z-Score
Target Scan	miR-7	209	V\$NRSF_01	141	21	6.80E-08	7.96
	miR-153	301	V\$NRSF_01	141	24	5.94E-07	4.80
	miR-381	444	V\$CHX10_01	176	34	1.38E-06	4.49
	miR-133	254	V\$NRSF_01	141	21	1.84E-06	5.64
	miR-448	302	V\$NRSF_01	141	23	2.35E-06	4.77
	miR-369-3p	295	V\$CDPCR1_01	87	17	3.05E-06	4.35
	miR-221	176	V\$CDPCR1_01	87	13	3.52E-06	5.60
	miR-135	292	V\$NRSF_01	141	22	4.79E-06	5.63
	miR-323	327	V\$NKX25_02	284	37	4.86E-06	3.89
	miR-103	271	V\$E47_02	11	6	5.46E-06	9.44
	miR-362	88	V\$TCF11MAF_01	132	11	7.49E-06	5.91
	miR-505	191	V\$CDPCR1_01	87	13	8.70E-06	5.20
	miR-362	88	V\$CDPCR1_01	87	9	9.29E-06	6.09

			01				
	miR-142-5p	319	V\$GATA1_05	141	22	1.99E-05	4.09
	miR-324-5p	70	V\$PAX6_01	153	10	2.18E-05	6.30
	miR-362	88	V\$P53_01	75	8	2.40E-05	7.76
	miR-324-5p	70	V\$HOX13_01	47	6	2.61E-05	7.02
	miR-503	202	V\$PAX6_Q2	92	13	2.96E-05	6.55
	miR-23	410	V\$NKX25_02	284	41	3.09E-05	3.35
	miR-129	163	V\$GFI1_01	132	14	3.48E-05	3.79
PicTar	hsa-miR-199a,b*	151	V\$CDPCR1_01	89	15	2.23E-09	8.58
	hsa-miR-326	261	V\$NRSF_01	154	25	3.30E-09	8.14
	hsa-miR-28	124	V\$AR_02	45	10	1.15E-08	9.26
	hsa-miR-369-3p	328	V\$CDPCR1_01	89	20	1.97E-08	6.81
	hsa-miR-153	359	V\$NRSF_01	154	27	1.32E-07	5.95
	hsa-miR-139	236	V\$POU1F1_Q6	177	23	1.56E-07	6.01
	hsa-miR-185	267	V\$PPARG_01	93	17	2.85E-07	6.52
	hsa-miR-199b	190	V\$TCF11MAFG_01	164	19	4.21E-07	5.60
	hsa-miR-328	207	V\$ARP1_01	86	14	6.66E-07	6.48
	hsa-miR-7	252	V\$NRSF_01	154	21	7.32E-07	5.86
	hsa-miR-186	415	V\$CDPCR1_01	89	20	9.45E-07	5.08
	hsa-miR-320	382	V\$CDPCR1_01	89	19	1.16E-06	5.90
	hsa-miR-142-5p	284	V\$GATA1_05	166	23	1.34E-06	5.19
	hsa-miR-132	191	V\$TEL2_Q6	85	13	1.42E-06	5.66
	hsa-miR-212	191	V\$TEL2_Q6	85	13	1.42E-06	6.32
	hsa-miR-133a,b*	333	V\$NRSF_01	154	24	1.57E-06	5.89
	hsa-miR-155	178	V\$EVI1_04	156	17	1.68E-06	6.15
	hsa-miR-139	236	V\$GATA2_01	18	7	2.21E-06	6.14
	hsa-miR-302a,d*	342	V\$ISRE_01	177	26	2.99E-06	5.46
	hsa-miR-135a	325	V\$NRSF_01	154	23	3.63E-06	5.37
	hsa-miR-10a	131	V\$POU6F1_01	302	20	3.74E-06	5.44

For Table 5, The *p*-value is a hypergeometric *p*-value for the co-occurrence of the a miR and a TF in the 3' UTRs and promoters of the same genes, and the Z-score is assigned

according to the randomization based co-occurrence method. The Table depicts the number of targets each of miR and each TF, and the number of targets which contain sites for both miR and TF.

*In the PicTar table, the pairs of duplicated miRs (a,b etc.) were unified when they appeared more than once as significant.

The full networks of TF-miR partners are presented in Tables 6-8

Table 6

mi R	target num	TF	target num	intersection size	hyper-geometric co-occurrence p-value	Z-score	significant FDR level (q-value)	corresponding FDR p-val	network motifs - FFLs	
									TF->miR	miR->TF
mi R-7	209	V\$NR SF_01	141	21	6.80E-08	7.9595	0.1	3.48E-05		TFs unmapped
mi R-153	301	V\$NR SF_01	141	24	5.94E-07	4.7958	0.1	3.48E-05		TFs unmapped
mi R-381	444	V\$CH X10_01	176	34	1.38E-06	4.4886	0.1	3.48E-05		
mi R-133	254	V\$NR SF_01	141	21	1.84E-06	5.6409	0.1	3.48E-05		TFs unmapped
mi R-448	302	V\$NR SF_01	141	23	2.35E-06	4.7665	0.1	3.48E-05		TFs unmapped
mi R-369-3p	295	V\$CD PCR1_01	87	17	3.05E-06	4.3523	0.1	3.48E-05		
mi R-221	176	V\$CD PCR1_01	87	13	3.52E-06	5.6045	0.1	3.48E-05		
mi R-135	292	V\$NR SF_01	141	22	4.79E-06	5.634	0.1	3.48E-05		TFs unmapped
mi R-323	327	V\$NK X25_02	284	37	4.86E-06	3.8887	0.1	3.48E-05		TFs unmapped
mi R-103	271	V\$E4 7_02	11	6	5.46E-06	9.4438	0.1	3.48E-05		TFs unmapped
mi R-362	88	V\$TC F11M AFG_01	132	11	7.49E-06	5.9118	0.1	3.48E-05		
mi R-505	191	V\$CD PCR1_01	87	13	8.70E-06	5.2038	0.1	3.48E-05		
mi R-362	88	V\$CD PCR1_01	87	9	9.29E-06	6.091	0.1	3.48E-05		
mi R-142-5p	319	V\$GATA1_05	141	22	1.99E-05	4.094	0.1	3.48E-05	V\$GATA1_05 ==>miR-142-5p in	

									cluster cluster 113_hsa- mir-142	
mi R- 324 -5p	70	V\$PA X6_01	153	10	2.18E-05	6.3003	0.1	3.48E- 05		
mi R- 362	88	V\$P53 _01	75	8	2.40E-05	7.7645	0.1	3.48E- 05		
mi R- 324 -5p	70	V\$HO X13_0 1	47	6	2.61E-05	7.0234	0.1	3.48E- 05		TFs unmapped
mi R- 503	202	V\$PA X6_Q 2	92	13	2.96E-05	6.5452	0.1	3.48E- 05		
mi R- 23	410	V\$NK X25_0 2	284	41	3.09E-05	3.3474	0.1	3.48E- 05		TFs unmapped
mi R- 129	163	V\$GF I1_01	132	14	3.48E-05	3.7906	0.1	3.48E- 05		TFs unmapped
mi R- 448	302	V\$CD P_02	262	31	4.23E-05	2.9089	0.2	0.00021 675		
mi R- 380 -5p	37	V\$AF P1_Q6	199	8	4.36E-05	5.3163	0.2	0.00021 675		TFs unmapped
mi R- 186	333	V\$PO U6F1_ 01	261	33	4.46E-05	3.2556	0.2	0.00021 675		TFs unmapped
mi R- 369 -3p	295	V\$NK X25_0 2	284	32	5.26E-05	3.1089	0.2	0.00021 675		TFs unmapped
mi R- 190	69	V\$SR F_Q5_ 02	107	8	5.39E-05	5.3161	0.2	0.00021 675		
mi R-7	209	V\$CD P_02	262	24	5.62E-05	4.983	0.2	0.00021 675	V\$CDP CR3_01, V\$CDP_ 01, V\$CDP_ 02==> miR-7 in cluster cluster26 7_hsa- mir-7-1	
mi R- 10	116	V\$IRF 2_01	146	12	5.64E-05	5.4582	0.2	0.00021 675	V\$IRF2_ 01==> miR-10 in cluster cluster11 1_hsa- mir-10a	
mi R- 93	305	V\$E2 F_Q3_ 01	9	5	5.65E-05	7.2658	0.2	0.00021 675	V\$E2F_ 01,V\$E2 F_03 ==>miR- 93 in	

									cluster	
									cluster23 8_hsa- mir-106b	
mi R- 342	103	V\$NK X61_0 1	140	11	5.91E-05	5.778	0.2	0.00021 675		
mi R- 153	301	V\$AL X4_01	127	19	6.03E-05	4.1324	0.2	0.00021 675		
mi R- 19	460	V\$SR F_Q6	71	17	6.18E-05	5.339	0.2	0.00021 675		
mi R- 369 -3p	295	V\$GA TA_C	98	16	6.28E-05	4.3958	0.2	0.00021 675		miR-369- 3p==> TF cluster 110: V\$GATA3 _01, V\$GATA_ C, (NM_0020 51)
mi R- 185	112	V\$CD PCR1 _01	87	9	6.53E-05	4.2658	0.2	0.00021 675		
mi R- 369 -3p	295	V\$CH X10_0 1	176	23	6.67E-05	3.4794	0.2	0.00021 675		
mi R- 15	464	V\$PA X6_Q 2	92	20	7.09E-05	4.2593	0.2	0.00021 675		
mi R- 93	305	V\$ISR E_01	160	22	7.30E-05	3.4146	0.2	0.00021 675		TFs unmapped
mi R- 185	112	V\$TC F1 1MAF G_01	132	11	7.48E-05	4.6618	0.2	0.00021 675		
mi R- 503	202	V\$CD PCR1 _01	87	12	7.69E-05	4.2765	0.2	0.00021 675	V\$CDP_ 02==>mi R-503 in cluster cluster29 3 _hsa- mir-424	
mi R- 219	159	V\$PO U1F1_ Q6	148	14	9.42E-05	3.9043	0.2	0.00021 675		
mi R- 129	163	V\$NK X3A_ 01	110	12	9.78E-05	4.1481	0.2	0.00021 675		
mi R- 30	570	V\$IRF _Q6	154	32	0.0001	2.9862	0.2	0.00021 675		miR- 30==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6 _01, (NM_0024 60)
mi R- 362	88	V\$PA X6_Q 2	92	8	0.000106	5.1596	0.2	0.00021 675		

mi R-15	464	V\$CDX2_Q5	222	36	0.000107	3.8872	0.2	0.00021675		TFs unmapped
mi R-539	245	V\$CHX10_01	176	20	0.00011	3.3106	0.2	0.00021675		
mi R-139	162	V\$POU1F1_Q6	148	14	0.000115	3.9767	0.2	0.00021675		
mi R-10	116	V\$POU6F1_01	261	16	0.000116	5.4943	0.2	0.00021675	V\$POU6F1_01==>miR-10 in cluster cluster111_hsa-mir-10a V\$POU6F1_01==>miR-10 in cluster cluster146_hsa-mir-10b	TFs unmapped
mi R-33	158	V\$NXX25_01	193	16	0.000134	3.7124	0.2	0.00021675		TFs unmapped
mi R-185	112	V\$P53_01	75	8	0.000136	5.2727	0.2	0.00021675		
mi R-410	311	V\$NXX25_02	284	32	0.000146	3.2331	0.2	0.00021675		TFs unmapped
mi R-223	123	V\$PBX1_02	108	10	0.000146	4.3486	0.2	0.00021675		TFs unmapped
mi R-494	212	V\$HSF1_01	41	8	0.000148	5.5316	0.2	0.00021675		
mi R-7	209	V\$SELF1_Q6	65	10	0.000161	4.6964	0.2	0.00021675		
mi R-144	363	V\$HNF3_Q6	79	15	0.000185	4.154	0.2	0.00021675		
mi R-33	158	V\$S8_01	122	12	0.000197	3.8099	0.2	0.00021675		TFs unmapped
mi R-448	302	V\$ALX4_01	127	18	0.0002	3.879	0.2	0.00021675		
mi R-431	64	V\$NXX61_01	140	8	0.000209	4.9254	0.2	0.00021675		
mi R-28	74	V\$FOXO4_02	226	11	0.000209	4.8567	0.2	0.00021675		
mi R-192	68	V\$MMEF2_Q6	132	8	0.000214	4.7816	0.2	0.00021675		
mi R-194	167	V\$STST1_01	134	13	0.000214	3.461	0.2	0.00021675		
mi R-	71	V\$HIF1_Q5	43	5	0.000217	5.3366	0.2	0.00021675		

382										
mi R-219	159	V\$AT F3_Q6	123	12	0.000226	3.6894	0.3	0.00058 879		
mi R-326	179	V\$CD X_Q5	197	17	0.000233	3.8671	0.3	0.00058 879		
mi R-494	212	V\$CI Z_01	55	9	0.000236	4.276	0.3	0.00058 879		TFs unmapped
mi R-19	460	V\$TC F1 1MAF G_01	132	24	0.00024	4.0182	0.3	0.00058 879		
mi R-221	176	V\$FO X_Q2	112	12	0.000241	4.4253	0.3	0.00058 879		miR- 221==> TF cluster 83: V\$FOX_Q 2, (NM_0021 58)
mi R-133	254	V\$AL X4_01	127	16	0.000249	4.3241	0.3	0.00058 879		
mi R-135	292	V\$E2 F_Q4	33	8	0.000271	3.7875	0.3	0.00058 879		TFs unmapped
mi R-329	151	V\$TC F1 1MAF G_01	132	12	0.000271	3.9531	0.3	0.00058 879		
mi R-141	287	V\$TA TA_0 1	81	13	0.000279	4.0233	0.3	0.00058 879		
mi R-148	292	V\$FO X_Q2	112	16	0.000281	4.6302	0.3	0.00058 879		miR- 148==> TF cluster 83: V\$FOX_Q 2, (NM_0045 14)
mi R-324 -5p	70	V\$AI RE_02	169	9	0.000281	4.6496	0.3	0.00058 879		
mi R-362	88	V\$PA X2_01	57	6	0.000285	6.0276	0.3	0.00058 879		
mi R-1	349	V\$CR EBP1 CJUN _01	59	12	0.000293	4.5982	0.3	0.00058 879		
mi R-93	305	V\$CD PCR1 _01	87	14	0.000299	3.598	0.3	0.00058 879		
mi R-30	570	V\$HI F1_Q5	43	13	0.000305	3.5151	0.3	0.00058 879		
mi R-323	327	V\$CD C5_01	187	24	0.000307	4.0063	0.3	0.00058 879		
mi R-369 -3p	295	V\$PO U6F1_ 01	261	28	0.000362	2.4956	0.3	0.00058 879		TFs unmapped
mi	68	V\$PP	77	6	0.000363	4.6081	0.3	0.00058		TFs

R-383		ARG_01						879		unmapped
mi R-192	68	V\$FO XJ2_02	263	11	0.000364	4.3486	0.3	0.00058879		
mi R-22	195	V\$SR F_Q4	28	6	0.000386	4.6782	0.3	0.00058879		miR-22==> TF cluster 267: V\$SRF_01, V\$SRF_C, V\$SRF_Q4, V\$SRF_Q5_01, V\$SRF_Q5_02, V\$SRF_Q6, (NM_003131)
mi R-326	179	V\$SO X5_01	84	10	0.000392	4.1176	0.3	0.00058879		
mi R-375	128	V\$H MGIY_Q3	117	10	0.000392	4.4377	0.3	0.00058879		
mi R-448	302	V\$HN F6_Q6	349	35	0.000395	3.8394	0.3	0.00058879		
mi R-218	358	V\$PO U6F1_01	261	32	0.000406	3.3305	0.3	0.00058879		TFs unmapped
mi R-26	404	V\$PO U3F2_02	344	43	0.000409	3.2231	0.3	0.00058879		
mi R-377	178	V\$E4 BP4_01	208	17	0.000416	4.0263	0.3	0.00058879		TFs unmapped
mi R-376	101	V\$E4 BP4_01	208	12	0.000427	5.1605	0.3	0.00058879		TFs unmapped
mi R-29	465	V\$PA X_Q6	112	21	0.000438	3.729	0.3	0.00058879		
mi R-93	305	V\$PR_02	51	10	0.000438	5.5509	0.3	0.00058879	V\$PR_01==>mi R-93 in cluster cluster238 _hsa-mir-106b	TFs unmapped
mi R-410	311	V\$IRF_Q6	154	20	0.000439	3.3209	0.3	0.00058879		
mi R-34	278	V\$ZI C2_01	66	11	0.000449	3.9019	0.3	0.00058879		
mi R-19	460	V\$IRF_Q6	154	26	0.000453	3.6245	0.3	0.00058879		
mi R-505	191	V\$HN F6_Q6	349	25	0.00046	3.7077	0.3	0.00058879	V\$HNF6_Q6==> miR-505 in cluster	

									cluster29 5_hsa- mir-505	
mi R- 410	311	V\$HN F3 ALPH A_Q6	69	12	0.000462	3.8187	0.3	0.00058 879		
mi R- 221	176	V\$AR _02	32	6	0.000478	5.164	0.3	0.00058 879		
mi R- 382	71	V\$HT F_01	109	7	0.0005	5.1437	0.3	0.00058 879		TFs unmapped
mi R- 130	337	V\$NF Y_C	144	20	0.000511	3.3669	0.3	0.00058 879	V\$ALP HACP1_ 01==> miR-130 in cluster cluster41 _hsa-m ir-130a V\$ALP HACP1_ 01, V\$NFY_ 01==>mi R-130 in cluster cluster17 0 _hsa- mir-130b	
mi R- 210	10	V\$ZF 5_B	92	3	0.000518	10.159	0.3	0.00058 879		TFs unmapped
mi R- 183	186	V\$SO X5_01	84	10	0.000531	3.8729	0.3	0.00058 879	V\$SOX_ Q6==> miR-183 in cluster cluster24 2_hsa- mir-183	
mi R- 28	74	V\$AH R_Q5	50	5	0.000539	5.2262	0.3	0.00058 879		
mi R- 93	305	V\$PA X6_Q 2	92	14	0.000541	4.1823	0.3	0.00058 879		
mi R- 33	158	V\$CH X10_0 1	176	14	0.000545	3.9391	0.3	0.00058 879		
mi R- 185	112	V\$PA X6_Q 2	92	8	0.000562	4.1788	0.3	0.00058 879		
mi R- 185	112	V\$SR F_Q6	71	7	0.000589	4.4265	0.3	0.00058 879		

Table 6 - miR-TF significantly co-occurring pairs in the TargetScan network.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value <10E-3 in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfbsConsFactors track.

Table 7

miR	target num	TF	target num	intersection size	hyper-geometric co-occurrence p-value	Z-score	significant FDR level (q-value)	corresponding FDR p-val	network motifs - FFLs	
									TF->miR	miR->TF
hsa-miR-199a	151	V\$CDP CR1_01	89	15	2.23E-09	8.5788	0.1	0.00038 368		
hsa-miR-326	261	V\$NRS F_01	154	25	3.30E-09	8.1413	0.1	0.00038 368		TFs unmapped
hsa-miR-28	124	V\$AR_02	45	10	1.15E-08	9.2604	0.1	0.00038 368		
hsa-miR-369-3p	328	V\$CDP CR1_01	89	20	1.97E-08	6.81	0.1	0.00038 368		
hsa-miR-199b	190	V\$CDP CR1_01	89	15	5.22E-08	6.4992	0.1	0.00038 368		
hsa-miR-153	359	V\$NRS F_01	154	27	1.32E-07	5.9486	0.1	0.00038 368		TFs unmapped
hsa-miR-139	236	V\$POU 1F1_Q6	177	23	1.56E-07	6.0075	0.1	0.00038 368		
hsa-miR-185	267	V\$PPA RG_01	93	17	2.85E-07	6.5248	0.1	0.00038 368		TFs unmapped
hsa-miR-199b	190	V\$TCF 11MAF G_01	164	19	4.21E-07	5.6021	0.1	0.00038 368		hsa-miR-199b==> TF cluster 162: V\$MAF

										Q6_01, V\$TCF11 MAFG_0 1, V\$TCF11 _01, (NM_003 204)
hsa-miR-328	207	V\$ARP 1_01	86	14	6.66E-07	6.4786	0.1	0.00038 368		
hsa-miR-7	252	V\$NRS F_01	154	21	7.32E-07	5.864	0.1	0.00038 368		TFs unmapped
hsa-miR-186	415	V\$CDP CR1_01	89	20	9.45E-07	5.0821	0.1	0.00038 368		
hsa-miR-320	382	V\$CDP CR1_01	89	19	1.16E-06	5.9036	0.1	0.00038 368		
hsa-miR-142-5p	284	V\$GAT A1_05	166	23	1.34E-06	5.1857	0.1	0.00038 368	V\$G ATA 1_05 => hsa-miR-142-5p in cluster113_hsa-mir-142	
hsa-miR-132	191	V\$TEL 2_Q6	85	13	1.42E-06	5.661	0.1	0.00038 368		
hsa-miR-212	191	V\$TEL 2_Q6	85	13	1.42E-06	6.3185	0.1	0.00038 368		
hsa-miR-133b	333	V\$NRS F_01	154	24	1.57E-06	5.8896	0.1	0.00038 368		TFs unmapped
hsa-miR-155	178	V\$EVI1 _04	156	17	1.68E-06	6.15	0.1	0.00038 368		TFs unmapped
hsa-miR-139	236	V\$GAT A2_01	18	7	2.21E-06	6.1369	0.1	0.00038 368		TFs unmapped
hsa-miR-133a	318	V\$NRS F_01	154	23	2.50E-06	5.8745	0.1	0.00038 368		TFs unmapped
hsa-miR-302a	342	V\$ISRE _01	177	26	2.99E-06	5.4579	0.1	0.00038 368		TFs unmapped
hsa-miR-	325	V\$NRS F_01	154	23	3.63E-06	5.3694	0.1	0.00038 368		TFs unmapped

135a										
hsa-miR-302d	346	V\$ISRE_01	177	26	3.71E-06	5.0271	0.1	0.00038368		TFs unmapped
hsa-miR-10a	131	V\$POU6F1_01	302	20	3.74E-06	5.4437	0.1	0.00038368	V\$POU6F1_01=>hsa-miR-10a in cluster cluster111_hsa-mir-10a	TFs unmapped
hsa-miR-10b	131	V\$POU6F1_01	302	20	3.74E-06	6.0644	0.1	0.00038368	V\$POU6F1_01=>hsa-miR-10b in cluster cluster146_hsa-mir-10b	TFs unmapped
hsa-miR-369-3p	328	V\$CDC5_01	222	29	3.84E-06	4.577	0.1	0.00038368		
hsa-miR-302d	346	V\$PBX1_01	87	17	4.00E-06	5.246	0.1	0.00038368		TFs unmapped
hsa-miR-10a	131	V\$HNF1_01	179	15	4.08E-06	5.0633	0.1	0.00038368		
hsa-miR-10b	131	V\$HNF1_01	179	15	4.08E-06	5.8872	0.1	0.00038368		
hsa-miR-218	417	V\$CDPCR1_01	89	19	4.31E-06	5.8815	0.1	0.00038368	V\$CDPCR1_01=>hsa-miR-218 in	

									cluster cluster21 6_hsa- mir- 218- 2	
hsa-miR-135b	329	V\$NRS F_01	154	23	4.46E-06	5.9019	0.1	0.00038 368		TFs unmapped
hsa-miR-302b	314	V\$PBX 1_01	87	16	5.04E-06	5.4742	0.1	0.00038 368		TFs unmapped
hsa-miR-185	267	V\$TCF 11MAF G_01	164	21	5.27E-06	5.4573	0.1	0.00038 368		
hsa-miR-19b	520	V\$SRF _Q6	87	21	5.63E-06	5.331	0.1	0.00038 368		
hsa-miR-302c	312	V\$E2F Q3_01	7	5	5.76E-06	10.750 2	0.1	0.00038 368		
hsa-miR-199a	151	V\$PAX 6_Q2	121	13	5.80E-06	5.234	0.1	0.00038 368	V\$P AX_ Q6= =>hs a- miR- 199a in cluster cluster12 8_hsa- mir- 199a -1	
hsa-miR-302b	314	V\$E2F Q3_01	7	5	5.94E-06	10.516 3	0.1	0.00038 368		
hsa-miR-302c	312	V\$ISRE _01	177	24	6.12E-06	5.3246	0.1	0.00038 368		TFs unmapped
hsa-miR-19a	523	V\$SRF _Q6	87	21	6.17E-06	5.1441	0.1	0.00038 368		
hsa-miR-206	400	V\$E12_ Q6	18	8	6.42E-06	5.7796	0.1	0.00038 368		
hsa-miR-324-5p	48	V\$HOX 13_01	62	6	6.54E-06	8.9039	0.1	0.00038 368		TFs unmapped
hsa-miR-	402	V\$E12_ Q6	18	8	6.66E-06	4.5882	0.1	0.00038 368		

1										
hsa-miR-30b	624	V\$IRF_Q6	170	36	7.98E-06	4.089	0.1	0.00038368		hsa-miR-30b==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
hsa-miR-30c	624	V\$IRF_Q6	170	36	7.98E-06	4.3065	0.1	0.00038368		hsa-miR-30c==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
hsa-miR-199a	151	V\$TCF11MAFG_01	164	15	8.12E-06	4.9904	0.1	0.00038368		hsa-miR-199a==> TF cluster 162: V\$MAF_Q6_01, V\$TCF11MAFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-30a-5p	625	V\$IRF_Q6	170	36	8.27E-06	4.271	0.1	0.00038368		hsa-miR-30a-5p==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
hsa-miR-9-star	300	V\$HNF3ALPHA_Q6	84	15	8.37E-06	4.3411	0.1	0.00038368		
hsa-miR-30d	626	V\$IRF_Q6	170	36	8.58E-06	4.5803	0.1	0.00038368		hsa-miR-30d==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)

hsa-miR-302a	342	V\$E2F_Q3_01	7	5	9.06E-06	10.7872	0.1	0.00038368		
hsa-miR-28	124	V\$AP1_Q2_01	71	9	9.28E-06	5.5825	0.1	0.00038368	V\$AP1_Q2_01=>hsa-miR-28 in cluster191_hsa-mir-28	
hsa-miR-369-3p	328	V\$CHX10_01	196	26	9.38E-06	4.2096	0.1	0.00038368		
hsa-miR-30e-5p	629	V\$IRF_Q6	170	36	9.56E-06	3.6723	0.1	0.00038368		hsa-miR-30e-5p=> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
hsa-miR-302d	346	V\$E2F_Q3_01	7	5	9.60E-06	9.3775	0.1	0.00038368		
hsa-miR-368	110	V\$OCT1_07	262	16	1.13E-05	6.0062	0.1	0.00038368		
hsa-miR-135a	325	V\$SPZ1_01	37	10	1.23E-05	5.6836	0.1	0.00038368		TFs unmapped
hsa-miR-328	207	V\$AR_02	45	9	1.25E-05	6.2954	0.1	0.00038368		
hsa-miR-10b	131	V\$ETS_Q4	16	5	1.35E-05	5.9475	0.1	0.00038368		
hsa-miR-10a	131	V\$ETS_Q4	16	5	1.35E-05	6.6525	0.1	0.00038368		
hsa-miR-135b	329	V\$SPZ1_01	37	10	1.37E-05	5.6531	0.1	0.00038368		TFs unmapped
hsa-miR-323	246	V\$AFP1_Q6	220	23	1.46E-05	4.8366	0.1	0.00038368		TFs unmapped
hsa-	342	V\$PBX	87	16	1.50E-	4.72	0.1	0.00038		TFs

miR-302a		1_01			05			368		unmapped
hsa-miR-186	415	V\$POU6F1_01	302	40	1.54E-05	3.7425	0.1	0.00038368		TFs unmapped
hsa-miR-335	136	V\$ETS_Q4	16	5	1.62E-05	7.4903	0.1	0.00038368		
hsa-miR-190	91	V\$CDC5_01	222	13	1.63E-05	5.9318	0.1	0.00038368		
hsa-miR-28	124	V\$PR_02	76	9	1.63E-05	5.8989	0.1	0.00038368		TFs unmapped
hsa-miR-135a	325	V\$E12_Q6	18	7	1.84E-05	5.6157	0.1	0.00038368		
hsa-miR-28	124	V\$PIT_X2_Q2	164	13	1.87E-05	5.9985	0.1	0.00038368		
hsa-miR-144	428	V\$FOX_P1_01	195	30	1.91E-05	4.2977	0.1	0.00038368		TFs unmapped
hsa-miR-135b	329	V\$E12_Q6	18	7	2.00E-05	5.1372	0.1	0.00038368		
hsa-miR-190	91	V\$CAR_T1_01	335	16	2.08E-05	5.1666	0.1	0.00038368		
hsa-miR-10b	131	V\$IRF2_01	157	13	2.12E-05	5.249	0.1	0.00038368		
hsa-miR-302b	314	V\$ISRE_01	177	23	2.17E-05	4.473	0.1	0.00038368		TFs unmapped
hsa-miR-302d	346	V\$CDP_CR1_01	89	16	2.33E-05	4.7017	0.1	0.00038368		
hsa-miR-142-5p	284	V\$SPZ_1_01	37	9	2.90E-05	5.9403	0.1	0.00038368		TFs unmapped
hsa-miR-302b	314	V\$CDP_CR1_01	89	15	2.97E-05	4.6485	0.1	0.00038368		
hsa-miR-144	428	V\$POU6F1_01	302	40	3.17E-05	3.3727	0.1	0.00038368		TFs unmapped
hsa-miR-222	208	V\$CDP_CR1_01	89	12	3.28E-05	5.2806	0.1	0.00038368		
hsa-miR-129	204	V\$NKX62_Q2	153	16	3.32E-05	4.3738	0.1	0.00038368		
hsa-miR-9	614	V\$NFY_Q6_01	28	11	3.33E-05	4.4212	0.1	0.00038368		
hsa-miR-	359	V\$CDP_CR1_01	89	16	3.67E-05	4.3352	0.1	0.00038368		

153										
hsa-miR-15a	585	V\$PAX 6_Q2	121	26	3.77E-05	3.6131	0.1	0.00038 368		
hsa-miR-23b	395	V\$POU 3F2_Q2	388	45	3.83E-05	3.4657	0.1	0.00038 368		
hsa-miR-155	178	V\$FRE AC2_Q1	217	18	3.88E-05	4.7036	0.1	0.00038 368		
hsa-miR-199a -star	420	V\$POU 1F1_Q6	177	27	4.19E-05	3.9328	0.1	0.00038 368		
hsa-miR-23a	391	V\$TGIF F_Q1	101	18	4.30E-05	4.4038	0.1	0.00038 368	hsa-miR-23a==> TF cluster 291: V\$TGIF_Q1, (NM_003244)	
hsa-miR-155	178	V\$HNF 1_Q1	179	16	4.32E-05	4.8838	0.1	0.00038 368		
hsa-miR-28	124	V\$ARP 1_Q1	86	9	4.46E-05	5.2267	0.1	0.00038 368		
hsa-miR-15b	592	V\$PAX 6_Q2	121	26	4.63E-05	4.1925	0.1	0.00038 368		
hsa-miR-28	124	V\$BAC H1_Q1	179	13	4.74E-05	5.4916	0.1	0.00038 368		
hsa-miR-206	400	V\$YY1 Q6	137	22	4.79E-05	4.4289	0.1	0.00038 368		
hsa-miR-193a	174	V\$E2F_ Q4	36	7	4.79E-05	5.5773	0.1	0.00038 368	TFs unmapped	
hsa-miR-23b	395	V\$TGIF F_Q1	101	18	4.92E-05	4.1178	0.1	0.00038 368	hsa-miR-23b==> TF cluster 291: V\$TGIF_Q1, (NM_003244)	
hsa-miR-221	217	V\$CDP CR1_Q1	89	12	4.98E-05	4.5877	0.1	0.00038 368		
hsa-miR-139	236	V\$FOX J2_Q1	137	16	5.02E-05	4.0258	0.1	0.00038 368		
hsa-miR-30a-5p	625	V\$HIF1 Q5	49	15	5.12E-05	4.3998	0.1	0.00038 368		
hsa-	626	V\$HIF1	49	15	5.22E-	4.5861	0.1	0.00038		

miR-30d		_Q5			05			368		
hsa-miR-368	110	V\$HM GIY_Q 3	123	10	5.30E-05	4.4145	0.1	0.00038 368		
hsa-miR-369-3p	328	V\$EVI1 _04	156	21	5.55E-05	4.1063	0.1	0.00038 368	TFs unmapped	
hsa-miR-328	207	V\$SP3_ Q3	80	11	5.59E-05	4.521	0.1	0.00038 368		
hsa-miR-144	428	V\$POU 1F1_Q6	177	27	5.82E-05	3.9948	0.1	0.00038 368		
hsa-miR-34b	246	V\$FRE AC4_01	208	21	5.88E-05	4.1436	0.1	0.00038 368		
hsa-miR-33	264	V\$S8_0 1	138	17	6.08E-05	4.9091	0.1	0.00038 368	TFs unmapped	
hsa-miR-194	186	V\$FOX _Q2	140	14	6.26E-05	3.8321	0.1	0.00038 368	hsa-miR-194==> TF cluster 96: V\$FOXO 1_02, V\$FOX_ Q2, (NM_002015)	
hsa-miR-23a	391	V\$POU 3F2_02	388	44	6.33E-05	3.4855	0.1	0.00038 368		
hsa-miR-326	261	V\$GCN F_01	140	17	6.34E-05	4.9127	0.1	0.00038 368		
hsa-miR-198	250	V\$ZID_ 01	92	13	6.40E-05	4.6917	0.1	0.00038 368	V\$Z ID_0 1== >hsa - miR- 198 in clust er clust er18 7_hs a- mir- 198	
hsa-miR-126-star	274	V\$PAX 6_Q2	121	16	6.59E-05	4.196	0.1	0.00038 368		
hsa-miR-190	190	V\$PAX 6_Q2	121	13	6.80E-05	4.5514	0.1	0.00038 368		

199b										
hsa-miR-324-5p	48	V\$PAX 6_01	188	8	7.67E-05	5.5386	0.1	0.00038 368		
hsa-miR-340	8	V\$PAX 4_03	11	2	7.81E-05	13.497 3	0.1	0.00038 368		TFs unmapped
hsa-miR-302a	342	V\$CDP CR1_01	89	15	7.98E-05	4.988	0.1	0.00038 368		
hsa-miR-323	246	V\$FOX J2_01	137	16	8.27E-05	4.7276	0.1	0.00038 368		
hsa-miR-16	577	V\$PAX 6_Q2	121	25	8.35E-05	3.8405	0.1	0.00038 368		
hsa-miR-302c	312	V\$PBX 1_01	87	14	8.65E-05	4.7986	0.1	0.00038 368		TFs unmapped
hsa-miR-182	501	V\$HNF 3ALPH A_Q6	84	18	8.68E-05	4.2334	0.1	0.00038 368		
hsa-miR-153	359	V\$MY OGNF1 _01	67	13	8.74E-05	4.3245	0.1	0.00038 368		
hsa-miR-206	400	V\$LM O2CO M_02	123	20	8.81E-05	4.6559	0.1	0.00038 368		
hsa-miR-186	415	V\$POU 1F1_Q6	177	26	9.10E-05	3.935	0.1	0.00038 368		
hsa-miR-1	402	V\$LM O2CO M_02	123	20	9.44E-05	3.9924	0.1	0.00038 368		
hsa-miR-302b	314	V\$CRE B_Q2	98	15	9.45E-05	4.075	0.1	0.00038 368		
hsa-miR-181c	476	V\$S8_0 1	138	24	9.50E-05	3.718	0.1	0.00038 368		TFs unmapped
hsa-miR-181a	476	V\$S8_0 1	138	24	9.50E-05	3.7271	0.1	0.00038 368		TFs unmapped
hsa-miR-182	501	V\$FRE AC2_01	217	34	9.64E-05	3.4548	0.1	0.00038 368		hsa-miR-182==> TF cluster 87: V\$FOX_ Q2, V\$FREA C2_01, (NM_001 452)
hsa-miR-10a	131	V\$IRF2 _01	157	12	9.79E-05	4.9299	0.1	0.00038 368	V\$I RF2 _01= =>hs a-	

									miR-10a in cluster cluster111_hsa-mir-10a	
hsa-miR-181b	477	V\$S8_01	138	24	9.82E-05	3.7243	0.1	0.00038368		TFs unmapped
hsa-miR-219	173	V\$POU1F1_Q6	177	15	0.00010033	3.8878	0.1	0.00038368		
hsa-miR-331	205	V\$NGFIC_01	86	11	0.00010062	5.2245	0.1	0.00038368		
hsa-miR-186	415	V\$PIT1_Q6	120	20	0.00010288	4.0933	0.1	0.00038368		
hsa-miR-195	585	V\$PAX6_Q2	121	25	0.00010442	4.1814	0.1	0.00038368		
hsa-miR-16	577	V\$CDX2_Q5	270	44	0.0001081	3.1462	0.1	0.00038368		TFs unmapped
hsa-miR-302c	312	V\$CDPCR1_01	89	14	0.0001115	4.2374	0.1	0.00038368		
hsa-miR-193b	171	V\$SRF_Q6	87	10	0.00011542	5.246	0.1	0.00038368		
hsa-miR-199b	190	V\$HNF3B_01	145	14	0.00011566	3.5103	0.1	0.00038368		TFs unmapped
hsa-miR-130b	474	V\$CDX2_Q5	270	38	0.00012048	3.7819	0.1	0.00038368		TFs unmapped
hsa-miR-193a	174	V\$PAX6_Q2	121	12	0.00012186	4.7132	0.1	0.00038368		
hsa-miR-149	208	V\$ETS_Q4	16	5	0.00012489	6.7867	0.1	0.00038368		
hsa-miR-369-3p	328	V\$NKX62_Q2	153	20	0.00012646	3.9413	0.1	0.00038368		
hsa-miR-23a	391	V\$IRF_Q6	170	24	0.0001265	3.5698	0.1	0.00038368		hsa-miR-23a==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6,

										V\$IRF_Q 6_01, hsa- miR- 23a==> TF cluster 151: V\$IRF2_0 1, V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 198 NM_0021 99)
hsa- miR- 101	429	V\$FOX P1_01	195	28	0.00013 168	3.6262	0.1	0.00038 368		TFs unmapped
hsa- miR- 194	186	V\$TST 1_01	150	14	0.00013 273	3.3743	0.1	0.00038 368		
hsa- miR- 193a	174	V\$SRF _Q6	87	10	0.00013 339	4.719	0.1	0.00038 368		
hsa- miR- 10a	131	V\$DR4 _Q2	94	9	0.00013 814	4.8362	0.1	0.00038 368		
hsa- miR- 10b	131	V\$DR4 _Q2	94	9	0.00013 814	5.1937	0.1	0.00038 368		
hsa- miR- 206	400	V\$IRF2 _01	157	23	0.00013 917	4.5543	0.1	0.00038 368		
hsa- miR- 302c -star	343	V\$OCT 1_01	159	21	0.00013 963	3.7483	0.1	0.00038 368	V\$O CT1 _06= =>hs a- miR- 302c -star in clust er clust er20 1_hs a- mir- 302b	
hsa- miR- 141	315	V\$STAT A_01	90	14	0.00013 972	4.046	0.1	0.00038 368		
hsa- miR- 193b	171	V\$CDP CR1_01	89	10	0.00013 996	4.9575	0.1	0.00038 368		
hsa- miR- 205	205	V\$VDR _Q3	48	8	0.00014 075	5.9189	0.1	0.00038 368		

331										
hsa-miR-183	219	V\$NFM UE1_Q 6	98	12	0.00014 129	4.8984	0.1	0.00038 368		TFs unmapped
hsa-miR-190	91	V\$SRF Q5_Q2	136	9	0.00014 317	4.7932	0.1	0.00038 368		
hsa-miR-9-star	300	V\$IRF7 _01	182	21	0.00014 685	3.6653	0.1	0.00038 368		
hsa-miR-23b	395	V\$IRF_Q6	170	24	0.00014 806	3.395	0.1	0.00038 368	hsa-miR-23b==> TF cluster 150: V\$IRF1_Q 1, V\$IRF_Q 6, V\$IRF_Q 6_Q1, hsa- miR- 23b==> TF cluster 151: V\$IRF2_Q 1, V\$IRF_Q 6, V\$IRF_Q 6_Q1, (NM_002 198 NM_0021 99)	
hsa-miR-33	264	V\$CDC 5_Q1	222	22	0.00014 871	4.144	0.1	0.00038 368		
hsa-miR-200c	441	V\$AIR E_Q2	201	29	0.00014 924	3.1757	0.1	0.00038 368		
hsa-miR-132	191	V\$TEF _Q6	185	16	0.00014 937	3.6899	0.1	0.00038 368		
hsa-miR-212	191	V\$TEF _Q6	185	16	0.00014 937	3.7721	0.1	0.00038 368		
hsa-miR-1	402	V\$IRF2 _01	157	23	0.00014 997	3.7434	0.1	0.00038 368		
hsa-miR-28	124	V\$RFX _Q6	79	8	0.00015 181	5.0315	0.1	0.00038 368		
hsa-miR-32	444	V\$AFP _Q6	220	31	0.00015 647	3.5478	0.1	0.00038 368		TFs unmapped
hsa-miR-101	429	V\$POU 1F1_Q6	177	26	0.00015 693	3.5295	0.1	0.00038 368		

hsa-miR-330	343	V\$OCT_C	297	32	0.0001573	3.3041	0.1	0.00038368		
hsa-miR-368	110	V\$CDP_01	197	12	0.0001583	4.3729	0.1	0.00038368		
hsa-miR-193a	174	V\$CDP_CR1_01	89	10	0.00016161	4.5398	0.1	0.00038368	V\$C DPC R3H D_0 1== >hsa - miR- 193a in clust er clust er10 7_hs a- mir- 193a	
hsa-miR-30b	624	V\$MEF_2_03	78	19	0.00016887	3.4163	0.1	0.00038368		
hsa-miR-30c	624	V\$MEF_2_03	78	19	0.00016887	3.8289	0.1	0.00038368	V\$H MEF 2_Q 6== >hsa - miR- 30c in clust er clust er5_ hsa- mir- 30e	
hsa-miR-222	208	V\$PAX_6_Q2	121	13	0.0001707	4.1628	0.1	0.00038368		
hsa-miR-135a	325	V\$IRF_Q6	170	21	0.00017075	3.6272	0.1	0.00038368		
hsa-miR-30a-5p	625	V\$MEF_2_03	78	19	0.00017248	4.022	0.1	0.00038368		
hsa-miR-194	186	V\$OCT_C	297	21	0.00017374	4.3649	0.1	0.00038368		
hsa-miR-30d	626	V\$MEF_2_03	78	19	0.00017616	3.5153	0.1	0.00038368		

hsa-miR-328	207	V\$PR_02	76	10	0.00017806	4.082	0.1	0.00038368		TFs unmapped
hsa-miR-28	124	V\$HNF3_Q6_01	81	8	0.00018108	5.0177	0.1	0.00038368		
hsa-miR-30e-5p	629	V\$MEF2_03	78	19	0.00018761	3.476	0.1	0.00038368	V\$HMEF2_Q6==>hsa-miR-30e-5p in cluster5_hsa-mir-30e	
hsa-miR-155	178	V\$IRF7_01	182	15	0.00018889	4.4025	0.1	0.00038368		
hsa-miR-199b	190	V\$SOX_Q6	152	14	0.00019154	4.003	0.1	0.00038368		
hsa-miR-33	264	V\$LUN1_01	97	13	0.00019314	4.5195	0.1	0.00038368		TFs unmapped
hsa-miR-368	110	V\$WHN_B	49	6	0.00019403	3.9715	0.1	0.00038368		TFs unmapped
hsa-miR-23b	395	V\$NKX25_02	331	38	0.00019653	3.3006	0.1	0.00038368		TFs unmapped
hsa-miR-301	468	V\$CDX2_Q5	270	37	0.0001985	3.4547	0.1	0.00038368		TFs unmapped
hsa-miR-301	468	V\$S8_01	138	23	0.00019895	3.5608	0.1	0.00038368		TFs unmapped
hsa-miR-206	400	V\$IRF_Q6_01	92	16	0.00020044	4.2935	0.1	0.00038368		
hsa-miR-33	264	V\$CHX10_01	196	20	0.00020141	4.2488	0.1	0.00038368		
hsa-miR-24	291	V\$AFP1_Q6	220	23	0.00020186	3.7786	0.1	0.00038368		TFs unmapped
hsa-miR-135b	329	V\$IRF_Q6	170	21	0.00020249	3.5913	0.1	0.00038368		
hsa-miR-30c	624	V\$HIF1_Q5	49	14	0.00020343	3.6624	0.1	0.00038368		
hsa-	624	V\$HIF1	49	14	0.00020	3.9858	0.1	0.00038		

miR-30b		_Q5			343			368		
hsa-miR-302a	342	V\$PR_02	76	13	0.00020424	4.0133	0.1	0.00038368		TFs unmapped
hsa-miR-30a-3p	226	V\$YY1_02	161	16	0.00020822	4.6717	0.1	0.00038368		
hsa-miR-1	402	V\$IRF_Q6_01	92	16	0.00021229	4.3434	0.1	0.00038368		
hsa-miR-148b	321	V\$S8_01	138	18	0.000216	3.393	0.1	0.00038368		TFs unmapped
hsa-miR-130a	488	V\$CDX2_Q5	270	38	0.0002208	3.1997	0.1	0.00038368		TFs unmapped
hsa-miR-30e-5p	629	V\$HIF1_Q5	49	14	0.0002214	4.2902	0.1	0.00038368		
hsa-miR-25	312	V\$ATF1_Q6	73	12	0.00022465	3.9149	0.1	0.00038368		
hsa-miR-9-star	300	V\$SRF_Q6	87	13	0.00022504	4.2639	0.1	0.00038368		
hsa-miR-199a-star	420	V\$FOX_P1_01	195	27	0.00022552	3.0817	0.1	0.00038368		TFs unmapped
hsa-miR-194	186	V\$FREAC3_01	238	18	0.00022637	4.1102	0.1	0.00038368		
hsa-miR-210	15	V\$HIF1_Q3	52	3	0.00022918	6.0322	0.1	0.00038368		
hsa-miR-93	541	V\$ISRE_01	177	30	0.00023048	3.4061	0.1	0.00038368		TFs unmapped
hsa-miR-103	580	V\$CDP_CR3HD_01	53	14	0.00023267	4.1768	0.1	0.00038368		
hsa-miR-34c	352	V\$FREAC4_01	208	25	0.00023273	3.3914	0.1	0.00038368		
hsa-miR-219	173	V\$LEF1_Q6	150	13	0.00023622	3.7491	0.1	0.00038368		TFs unmapped
hsa-miR-302c-star	343	V\$NKX61_01	165	21	0.0002366	3.9588	0.1	0.00038368		
hsa-miR-23a	391	V\$POU1F1_Q6	177	24	0.00023787	3.4577	0.1	0.00038368		
hsa-	208	V\$POU	177	16	0.00024	3.5483	0.1	0.00038		

miR-222		IF1_Q6			006			368		
hsa-miR-130b	474	V\$S8_01	138	23	0.00024006	3.6602	0.1	0.00038368		TFs unmapped
hsa-miR-328	207	V\$RFX_Q6	79	10	0.00024651	3.8327	0.1	0.00038368		
hsa-miR-103	580	V\$CDX2_Q5	270	43	0.00024653	3.2752	0.1	0.00038368		TFs unmapped
hsa-miR-135a	325	V\$ZIC2_01	71	12	0.00025065	4.4469	0.1	0.00038368		
hsa-miR-193b	171	V\$CREB_01	47	7	0.00025077	4.6925	0.1	0.00038368		
hsa-miR-218	417	V\$POU1F1_Q6	177	25	0.00025173	3.916	0.1	0.00038368		
hsa-miR-204	299	V\$MEF2_04	163	19	0.00025495	4.1189	0.1	0.00038368	V\$MEF2_01 => hsa-miR-204 in cluster cluster266_hsa-mir-204	
hsa-miR-375	160	V\$CDP_02	280	18	0.00025732	4.2264	0.1	0.00038368		
hsa-miR-148b	321	V\$FOX_Q2	140	18	0.00025927	3.3973	0.1	0.00038368		hsa-miR-148b=> TF cluster 83: V\$FOX_Q2, (NM_004514)
hsa-miR-221	217	V\$PAX6_Q2	121	13	0.00025979	4.065	0.1	0.00038368		
hsa-miR-368	110	V\$COMP1_01	73	7	0.00026761	4.1463	0.1	0.00038368		TFs unmapped
hsa-miR-107	588	V\$CDPCR3HD_01	53	14	0.00026868	4.3234	0.1	0.00038368		
hsa-miR-200b	440	V\$OCT1_01	159	24	0.00026898	3.0977	0.1	0.00038368	V\$OCT1_Q6	

									⇒ hsa-miR-200b in clust er clust er1_ hsa-mir-200b	
hsa-miR-153	359	V\$ALX 4_01	148	20	0.00027 011	3.8909	0.1	0.00038 368		
hsa-miR-342	143	V\$FOX J2_01	137	11	0.00027 093	4.2578	0.1	0.00038 368		
hsa-miR-299-3p	59	V\$IRF7 01	182	8	0.00027 26	4.9175	0.1	0.00038 368		
hsa-miR-302d	346	V\$CRE B_Q2	98	15	0.00027 688	3.4439	0.1	0.00038 368		
hsa-miR-193a	174	V\$CRE B_01	47	7	0.00027 908	5.2603	0.1	0.00038 368		
hsa-miR-135b	329	V\$ZIC2 _01	71	12	0.00028 074	3.9915	0.1	0.00038 368		
hsa-miR-199a	151	V\$FRE AC7_01	175	13	0.00028 262	4.3165	0.1	0.00038 368		
hsa-miR-323	246	V\$YY1 _Q6	137	15	0.00028 454	3.9147	0.1	0.00038 368		
hsa-miR-219	173	V\$NKK 62_Q2	153	13	0.00028 741	3.5716	0.1	0.00038 368		
hsa-miR-19b	520	V\$E4B P4_01	239	36	0.00028 945	3.3806	0.1	0.00038 368		TFs unmapped
hsa-miR-23a	391	V\$FOX J2_01	137	20	0.00029 284	3.3359	0.1	0.00038 368		
hsa-miR-182	501	V\$ZID _01	92	18	0.00029 337	4.118	0.1	0.00038 368		
hsa-miR-148b	321	V\$FOX J2_02	300	30	0.00029 439	2.9114	0.1	0.00038 368		
hsa-miR-148a	321	V\$FOX J2_02	300	30	0.00029 439	3.206	0.1	0.00038 368		
hsa-miR-195	585	V\$CDX 2_Q5	270	43	0.00029 774	2.8916	0.1	0.00038 368		TFs unmapped
hsa-	582	V\$SOX	152	28	0.00029	3.4322	0.1	0.00038		

miR-27a		_Q6			804			368		
hsa-miR-34a	351	V\$TCF 1P_Q6	87	14	0.00029 964	3.6973	0.1	0.00038 368		TFs unmapped
hsa-miR-212	191	V\$POU 1F1_Q6	177	15	0.00030 155	3.2373	0.1	0.00038 368		
hsa-miR-155	178	V\$FOX J2_Q2	300	20	0.00030 224	3.4167	0.1	0.00038 368		
hsa-miR-7	252	V\$ETS Q4	16	5	0.00030 782	5.5425	0.1	0.00038 368		
hsa-miR-302c -star	343	V\$CAR T1_Q1	335	34	0.00031 011	2.9099	0.1	0.00038 368		
hsa-miR-211	304	V\$MEF 2_Q4	163	19	0.00031 51	3.7236	0.1	0.00038 368		
hsa-miR-302b -star	240	V\$CDX Q5	240	21	0.00031 656	3.6563	0.1	0.00038 368		
hsa-miR-302c	312	V\$CRE B_Q2	98	14	0.00031 756	3.1423	0.1	0.00038 368		
hsa-miR-34b	246	V\$TEF Q6	185	18	0.00031 856	3.3902	0.1	0.00038 368		
hsa-miR-19a	523	V\$E4B P4_Q1	239	36	0.00032 376	3.4464	0.1	0.00038 368		TFs unmapped
hsa-miR-93	541	V\$PPA RA_Q2	65	15	0.00032 559	4.4361	0.1	0.00038 368	V\$D R4_ Q2, V\$P PAR A_Q 2== >hsa - miR- 93 in clust er clust er23 8_hs a- mir- 106b	hsa-miR-93==> TF cluster 229: V\$PPAR A_Q1, V\$PPAR A_Q2, V\$PPAR_ DR1_Q2, (NM_005 036)
hsa-miR-152	323	V\$FOX J2_Q2	300	30	0.00032 782	3.2255	0.1	0.00038 368		
hsa-miR-34a	351	V\$AIR E_Q2	201	24	0.00032 823	3.3975	0.1	0.00038 368		

hsa-miR-126-star	274	V\$CHX 10_01	196	20	0.00033 033	3.6113	0.1	0.00038 368		
hsa-miR-107	588	V\$OCT 1_03	54	14	0.00033 207	4.3952	0.1	0.00038 368		
hsa-miR-301	468	V\$NFY _C	161	25	0.00033 279	3.6735	0.1	0.00038 368		
hsa-miR-23a	391	V\$NKKX 25_02	331	37	0.00033 285	2.9799	0.1	0.00038 368		TFs unmapped
hsa-miR-331	205	V\$MZF 1_02	68	9	0.00033 443	4.1671	0.1	0.00038 368		
hsa-miR-183	219	V\$HMG IY_Q 3	123	13	0.00033 446	3.7824	0.1	0.00038 368		
hsa-miR-23b	395	V\$FOX J2_01	137	20	0.00033 485	3.1306	0.1	0.00038 368		
hsa-miR-186	415	V\$CRE B_Q4	102	17	0.00033 746	3.6143	0.1	0.00038 368		
hsa-miR-200b	440	V\$AIR E_02	201	28	0.00033 911	3.1959	0.1	0.00038 368		
hsa-miR-339	155	V\$CDP _01	197	14	0.00034 237	3.5478	0.1	0.00038 368		
hsa-miR-190	91	V\$GAT A1_04	121	8	0.00034 354	5.4111	0.1	0.00038 368		
hsa-miR-24	291	V\$PXR _Q2	49	9	0.00035 554	4.2233	0.1	0.00038 368		
hsa-miR-342	143	V\$NKKX 61_01	165	12	0.00035 885	5.0124	0.1	0.00038 368		
hsa-miR-218	417	V\$PAX 6_Q2	121	19	0.00036 055	4.0016	0.1	0.00038 368		
hsa-miR-28	124	V\$HP1 SITEFA CTOR_ Q6	219	13	0.00036 227	3.4981	0.1	0.00038 368		TFs unmapped
hsa-miR-196b	134	V\$PTF 1BETA _Q6	83	8	0.00036 537	4.3718	0.1	0.00038 368		TFs unmapped
hsa-miR-194	186	V\$OLF 1_01	46	7	0.00036 586	4.777	0.1	0.00038 368		TFs unmapped
hsa-miR-130a	488	V\$S8_0 1	138	23	0.00036 649	3.2025	0.1	0.00038 368		TFs unmapped
hsa-miR-190	91	V\$OCT 1_07	262	12	0.00036 93	4.0295	0.1	0.00038 368		

hsa-miR-193b	171	V\$E2F_Q4	36	6	0.00037481	4.6512	0.1	0.00038368		TFs unmapped
hsa-miR-339	155	V\$PAX4_04	91	9	0.00038338	4.6731	0.1	0.00038368		TFs unmapped
hsa-miR-153	359	V\$HNF6_Q6	403	40	0.00038368	3.2026	0.1	0.00038368	V\$HNF6_Q6=>hsa-miR-153 in cluster cluster247_hsa-mir-153-2	
hsa-miR-221	217	V\$POU1F1_Q6	177	16	0.00038812	3.6449	0.2	0.001708		
hsa-miR-10b	131	V\$IRF7_01	182	12	0.00039286	4.0385	0.2	0.001708		
hsa-miR-10a	131	V\$IRF7_01	182	12	0.00039286	4.5929	0.2	0.001708	V\$IRF7_01=>hsa-miR-10a in cluster cluster111_hsa-mir-10a	
hsa-miR-125a	375	V\$CREBATF_Q6	65	12	0.00039867	3.3075	0.2	0.001708		
hsa-miR-19b	520	V\$TCF11MAFG_01	164	27	0.00040299	3.4863	0.2	0.001708		
hsa-miR-130b	474	V\$NFYC	161	25	0.00040387	3.2246	0.2	0.001708	V\$ALPHACP1_01,V\$NFY_01=>hs	

									a-miR-130b in cluster cluster170_hsa-mir-130b	
hsa-miR-196a	136	V\$PTF1BETA_Q6	83	8	0.00040392	5.0314	0.2	0.001708		TFs unmapped
hsa-miR-28	124	V\$NFKB_Q6	91	8	0.00040568	4.7904	0.2	0.001708		
hsa-miR-135a	325	V\$E2F_Q4	36	8	0.0004075	3.7614	0.2	0.001708		TFs unmapped
hsa-miR-128b	507	V\$E2F_Q4	36	10	0.00040947	3.7421	0.2	0.001708		TFs unmapped
hsa-miR-92	413	V\$FOXO4_01	36	9	0.0004115	4.3782	0.2	0.001708		
hsa-miR-372	560	V\$ISRE_01	177	30	0.00041884	3.5076	0.2	0.001708		TFs unmapped
hsa-miR-331	205	V\$MYB_Q3	31	6	0.00042483	5.2422	0.2	0.001708		
hsa-miR-369-3p	328	V\$FOXJ2_02	300	30	0.00042662	3.5055	0.2	0.001708		
hsa-miR-183	219	V\$POU1F1_Q6	177	16	0.00043007	3.7782	0.2	0.001708		
hsa-miR-193b	171	V\$PAX6_Q2	121	11	0.00043214	4.6777	0.2	0.001708		
hsa-miR-128a	511	V\$E2F_Q4	36	10	0.00043622	3.6114	0.2	0.001708		TFs unmapped
hsa-miR-19a	523	V\$TCF11MAFG_01	164	27	0.00044157	3.5435	0.2	0.001708		
hsa-miR-135b	329	V\$E2F_Q4	36	8	0.00044255	3.9576	0.2	0.001708		TFs unmapped
hsa-miR-126-star	274	V\$CDPCR1_01	89	12	0.00045073	4.196	0.2	0.001708		
hsa-miR-26a	465	V\$POU3F2_02	388	47	0.00046804	3.2875	0.2	0.001708		

hsa-miR-206	400	V\$ZIC2_01	71	13	0.0004697	3.7028	0.2	0.001708		
hsa-miR-103	580	V\$HFH4_01	149	27	0.00047256	3.5815	0.2	0.001708		
hsa-miR-320	382	V\$POU3F2_01	201	25	0.00047685	3.1747	0.2	0.001708		
hsa-miR-342	143	V\$POU6F1_01	302	17	0.00047786	3.9023	0.2	0.001708		TFs unmapped
hsa-miR-29b	542	V\$E12_Q6	18	7	0.00047802	3.8916	0.2	0.001708		
hsa-miR-368	110	V\$CDC5_01	222	12	0.00047822	3.8829	0.2	0.001708		
hsa-miR-339	155	V\$ALP_HACP1_01	135	11	0.00047848	4.8393	0.2	0.001708		TFs unmapped
hsa-miR-183	219	V\$SOX5_01	96	11	0.00048042	3.6473	0.2	0.001708	V\$SOX_Q6=>hsa-miR-183 in cluster cluster24_2_hsa-mir-183	
hsa-miR-126-star	274	V\$OCT1_02	248	23	0.0004832	3.22	0.2	0.001708		
hsa-miR-185	267	V\$IRF_Q6_01	92	12	0.00048568	4.2825	0.2	0.001708		
hsa-miR-30a-3p	226	V\$OCT_Q6	282	22	0.0004884	3.2705	0.2	0.001708	V\$POU3F2_01=>hsa-miR-30a-3p in cluster cluster22_4_hsa-	hsa-miR-30a-3p in cluster 215: V\$OCT_Q6, (NM_006237)

									mir-30a	
hsa-miR-30e-3p	226	V\$OCT_Q6	282	22	0.0004884	3.2711	0.2	0.001708		hsa-miR-30e-3p=> TF cluster 215: V\$OCT_Q6, (NM_006237)
hsa-miR-1	402	V\$ZIC2_01	71	13	0.00049274	3.9208	0.2	0.001708		
hsa-miR-367	346	V\$FOXJ2_01	137	18	0.00049317	3.5324	0.2	0.001708		
hsa-miR-375	160	V\$FREAC7_01	175	13	0.00049698	4.1922	0.2	0.001708		
hsa-miR-10a	131	V\$WHN_B	49	6	0.00050004	3.521	0.2	0.001708		TFs unmapped
hsa-miR-142-3p	152	V\$YY1_02	161	12	0.00050154	3.8084	0.2	0.001708	V\$YY1_02=>hsa-miR-142-3p in cluster113_hsa-mir-142	
hsa-miR-29c	547	V\$E12_Q6	18	7	0.00050578	3.9527	0.2	0.001708		
hsa-miR-32	444	V\$ATF1_Q6	73	14	0.0005059	3.4088	0.2	0.001708		
hsa-miR-302c	312	V\$SOX_Q6	152	18	0.00050905	4.0368	0.2	0.001708		
hsa-miR-150	181	V\$CREBATF_Q6	65	8	0.00051554	4.0821	0.2	0.001708		
hsa-miR-21	135	V\$OCT1_05	264	15	0.00051618	3.8349	0.2	0.001708		
hsa-miR-221	217	V\$TCF11MAFG_01	164	15	0.00052084	3.4905	0.2	0.001708		
hsa-miR-	592	V\$CDPCR1_01	89	19	0.00052239	3.4899	0.2	0.001708	V\$CDP	

15b									02= =>hs a- miR- 15b in clust er clust er18 8_hs a- mir- 15b	
hsa- miR- 155	178	V\$CDC 5_01	222	16	0.00053 268	3.3985	0.2	0.00170 8		
hsa- miR- 208	59	V\$POU 3F2_01	201	8	0.00053 278	4.8805	0.2	0.00170 8		
hsa- miR- 9- star	300	V\$PTF 1BETA _Q6	83	12	0.00053 301	3.7495	0.2	0.00170 8		TFs unmapped
hsa- miR- 32	444	V\$ETS _Q4	16	6	0.00053 333	4.1619	0.2	0.00170 8		hsa-miR- 32==> TF cluster 72: V\$ETS_Q 4, (NM_002 017)
hsa- miR- 323	246	V\$POU 1F1_Q6	177	17	0.00054 292	3.4227	0.2	0.00170 8		
hsa- miR- 323	246	V\$PBX 1_01	87	11	0.00054 728	4.0101	0.2	0.00170 8		TFs unmapped
hsa- miR- 184	16	V\$E47_ 02	14	2	0.00054 734	7.5445	0.2	0.00170 8		TFs unmapped
hsa- miR- 302b	314	V\$SOX _Q6	152	18	0.00054 943	3.5774	0.2	0.00170 8		
hsa- miR- 125b	370	V\$MEF 2_03	78	13	0.00057 154	3.3461	0.2	0.00170 8		
hsa- miR- 340	8	V\$EVI1 _03	141	3	0.00057 635	6.2788	0.2	0.00170 8		TFs unmapped
hsa- miR- 24	291	V\$OCT _Q6	282	26	0.00058 186	3.0061	0.2	0.00170 8		
hsa- miR- 130b	474	V\$CDC 5_01	222	31	0.00058 403	3.3971	0.2	0.00170 8		
hsa- miR- 24	291	V\$DR3 _Q4	42	8	0.00058 587	4.4241	0.2	0.00170 8		
hsa-	360	V\$HNF	145	19	0.00058	3.0348	0.2	0.00170		TFs

miR-137		3B_01			745			8		unmapped
hsa-miR-194	186	V\$PAX 8_01	36	6	0.00058 75	4.5899	0.2	0.00170 8		
hsa-miR-93	541	V\$IRF_ Q6	170	28	0.00059 713	3.1772	0.2	0.00170 8		hsa-miR-93==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-93==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_01, (NM_002198 NM_002199)
hsa-miR-23b	395	V\$AFP 1_Q6	220	27	0.00060 051	3.2676	0.2	0.00170 8		TFs unmapped
hsa-miR-338	203	V\$OCT 1_01	159	14	0.00060 193	3.4866	0.2	0.00170 8		
hsa-miR-331	205	V\$CDP CR1_01	89	10	0.00060 491	3.8044	0.2	0.00170 8		
hsa-miR-137	360	V\$NKX 25_02	331	34	0.00060 644	2.7626	0.2	0.00170 8	V\$N KX2 5_02 => hsa-miR-137 in cluster cluster8_hsa-mir-137	TFs unmapped
hsa-miR-331	205	V\$DEC _Q1	59	8	0.00060 743	4.9574	0.2	0.00170 8		
hsa-miR-340	8	V\$HEN 1_01	30	2	0.00061 049	8.7888	0.2	0.00170 8		TFs unmapped

hsa-miR-219	173	V\$PBX 1_01	87	9	0.00061 373	3.5249	0.2	0.00170 8		TFs unmapped
hsa-miR-369-3p	328	V\$CAR T1_01	335	32	0.00061 865	2.5951	0.2	0.00170 8		
hsa-miR-26b	471	V\$POU 3F2_02	388	47	0.00062 367	3.1611	0.2	0.00170 8		
hsa-miR-130a	488	V\$NFY _C	161	25	0.00062 412	3.5499	0.2	0.00170 8	V\$A LPH ACP 1_01 => hsa-miR-130a in clust er clust er41 _hsa- mir-130a	
hsa-miR-93	541	V\$PR_ 02	76	16	0.00062 607	3.6701	0.2	0.00170 8	V\$P R_0 1= >hsa- miR-93 in clust er clust er23 8_hs a-mir-106b	TFs unmapped
hsa-miR-148a	321	V\$S8_0 1	138	17	0.00063 434	3.2566	0.2	0.00170 8		TFs unmapped
hsa-miR-34c	352	V\$TEF _Q6	185	22	0.00063 682	3.5053	0.2	0.00170 8		
hsa-miR-367	346	V\$FOX _Q2	140	18	0.00064 215	3.5483	0.2	0.00170 8	V\$F OX O4_ 02= =>hsa- miR-367 in clust er clust er20	hsa-miR-367=> TF cluster 83: V\$FOX_ Q2, (NM_002158)

									l_hs a- mir- 302b	
hsa-miR-96	544	V\$CREB_Q2	98	19	0.00064372	2.9232	0.2	0.001708	V\$CREB_Q2_01=>hsa-miR-96 in cluster242_hs a-mir-183	hsa-miR-96==> TF cluster 46: V\$CREB ATF_Q6, V\$CREB_Q1, V\$CREB_Q2, V\$CREB_Q2_01, V\$CREB_Q4, V\$CREB_Q4_01, V\$TAXC REB_Q1, V\$TAXC REB_Q2, (NM_004379)
hsa-miR-125a	375	V\$MEF2_Q3	78	13	0.00064917	3.1478	0.2	0.001708		
hsa-miR-103	580	V\$SOX_Q6	152	27	0.00065345	3.474	0.2	0.001708		
hsa-miR-367	346	V\$POU3F2_Q1	201	23	0.0006543	3.4002	0.2	0.001708	V\$POU3F2_Q1==>hsa-miR-367 in cluster201_hs a-mir-302b	
hsa-miR-28	124	V\$MAF_Q6	75	7	0.00065569	4.6881	0.2	0.001708		TFs unmapped
hsa-miR-30e-3p	226	V\$YY1_Q2	161	15	0.00065657	3.7852	0.2	0.001708		
hsa-miR-10a	131	V\$GAT_A1_Q5	166	11	0.00066204	4.2295	0.2	0.001708		

hsa-miR-10b	131	V\$GAT A1_05	166	11	0.00066 204	4.2781	0.2	0.00170 8		
hsa-miR-34b	246	V\$E2F1 Q3_01	19	5	0.00066 467	3.6372	0.2	0.00170 8		
hsa-miR-217	171	V\$CDP CR1_01	89	9	0.00066 703	3.7563	0.2	0.00170 8	V\$C DP_ 02= =>hs a- miR- 217 in clust er clust er14 3_hs a- mir- 216	
hsa-miR-214	412	V\$E47_ 01	31	8	0.00067 457	4.0563	0.2	0.00170 8		TFs unmapped
hsa-miR-32	444	V\$FOX O4_01	36	9	0.00070 029	4.9641	0.2	0.00170 8	V\$F OX O4_ 02= =>hs a- miR- 32 in clust er clust er27 0_hs a- mir- 32	
hsa-miR-206	400	V\$CRE BP1CJ UN_01	65	12	0.00071 384	3.9095	0.2	0.00170 8		
hsa-miR-325	23	V\$HIF1 Q5	49	3	0.00071 47	8.0569	0.2	0.00170 8		
hsa-miR-194	186	V\$YY1 Q6	137	12	0.00071 838	3.4613	0.2	0.00170 8		
hsa-miR-122a	116	V\$DEC Q1	59	6	0.00071 919	5.1785	0.2	0.00170 8		hsa-miR- 122a==> TF cluster 23: V\$DEC_ Q1, (NM_030 762)
hsa-	343	V\$HNF	179	21	0.00071	3.2068	0.2	0.00170		

miR-302c-star		1_01			948			8		
hsa-miR-19b	520	V\$IRF_Q6	170	27	0.00071979	3.0114	0.2	0.001708		
hsa-miR-29a	540	V\$TCF11MAF_G_01	164	27	0.00072831	3.3734	0.2	0.001708		
hsa-miR-1	402	V\$CREB_Q2_01	164	22	0.00072949	3.1809	0.2	0.001708		
hsa-miR-194	186	V\$POU1F1_Q6	177	14	0.00073596	3.0885	0.2	0.001708		
hsa-miR-96	544	V\$HNF3ALPHA_Q6	84	17	0.00073654	3.0936	0.2	0.001708		
hsa-miR-1	402	V\$CREBP1CJUN_01	65	12	0.00074627	3.6493	0.2	0.001708		
hsa-miR-20b	563	V\$GATA1_Q5	166	28	0.0007616	3.2574	0.2	0.001708		
hsa-miR-10b	131	V\$ATF1_Q6	73	7	0.00077282	3.7877	0.2	0.001708		
hsa-miR-10a	131	V\$ATF1_Q6	73	7	0.00077282	3.9785	0.2	0.001708		
hsa-miR-193b	171	V\$AP1_Q4	41	6	0.00077284	4.1755	0.2	0.001708		TFs unmapped
hsa-miR-194	186	V\$TGIF_01	101	10	0.00077374	3.7789	0.2	0.001708		hsa-miR-194==> TF cluster 291: V\$TGIF_01, (NM_003244)
hsa-miR-181a	476	V\$ETS_Q4	16	6	0.00077499	4.0731	0.2	0.001708		hsa-miR-181a==> TF cluster 72: V\$ETS_Q4, hsa-miR-181a==> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-	476	V\$ETS_Q4	16	6	0.00077499	4.2919	0.2	0.001708		hsa-miR-181c==>

181c										TF cluster 72: V\$ETS_Q 4, hsa- miR- 181c==> TF cluster 308: V\$ETS1_ B, V\$ETS_Q 4, (NM_005 238)
hsa- miR- 196a	136	V\$S8_0 1	138	10	0.00078 161	3.8071	0.2	0.00170 8		TFs unmapped
hsa- miR- 181b	477	V\$ETS Q4	16	6	0.00078 373	4.0559	0.2	0.00170 8		hsa-miR- 181b==> TF cluster 72: V\$ETS_Q 4, hsa- miR- 181b==> TF cluster 308: V\$ETS1_ B, V\$ETS_Q 4, (NM_005 238)
hsa- miR- 34b	246	V\$PAX 8 B	77	10	0.00078 706	4.1557	0.2	0.00170 8		
hsa- miR- 199b	190	V\$PAX 2 01	66	8	0.00078 902	4.0937	0.2	0.00170 8		
hsa- miR- 33	264	V\$EV11 05	72	10	0.00079 516	4.8417	0.2	0.00170 8		TFs unmapped
hsa- miR- 302a	342	V\$CRE B_Q2	98	14	0.00079 993	3.1576	0.2	0.00170 8		
hsa- miR- 17- 5p	565	V\$GAT A1_05	166	28	0.00080 532	2.7715	0.2	0.00170 8		
hsa- miR- 144	428	V\$HNF 3_Q6	88	15	0.00080 641	3.2656	0.2	0.00170 8		
hsa- miR- 107	588	V\$SOX Q6	152	27	0.00080 761	3.5452	0.2	0.00170 8		
hsa- miR- 199b	190	V\$FRE AC7_01	175	14	0.00081 174	2.9445	0.2	0.00170 8		
hsa-	205	V\$TFIII	144	13	0.00081	3.6066	0.2	0.00170		

miR-331		_Q6			592			8		
hsa-miR-146b	106	V\$STA T5A_01	91	7	0.00082 359	4.4518	0.2	0.00170 8	V\$S TAT _01, V\$S TAT _Q6 => hsa- miR- 146b in clust er clust er34 _hsa- mir- 146b	
hsa-miR-136	128	V\$HNF 4_01	55	6	0.00082 856	4.6119	0.2	0.00170 8		
hsa-miR-142-3p	152	V\$FOX P3_Q4	147	11	0.00083 335	3.6094	0.2	0.00170 8		
hsa-miR-144	428	V\$FOX O3_01	166	23	0.00083 851	3.1906	0.2	0.00170 8		
hsa-miR-302d	346	V\$PR_ 02	76	12	0.00084 142	3.6763	0.2	0.00170 8		TFs unmapped
hsa-miR-215	75	V\$POU 6F1_01	302	11	0.00084 479	5.0843	0.2	0.00170 8		TFs unmapped
hsa-miR-193a	174	V\$AP1 Q4	41	6	0.00084 681	4.1189	0.2	0.00170 8		TFs unmapped
hsa-miR-302b	314	V\$ATF 4_Q2	32	7	0.00084 774	4.7736	0.2	0.00170 8		
hsa-miR-27a	582	V\$HNF 1_C	154	27	0.00084 906	2.8933	0.2	0.00170 8		
hsa-miR-27b	590	V\$SOX _Q6	152	27	0.00085 081	3.0047	0.2	0.00170 8		
hsa-miR-19b	520	V\$PAX 6_Q2	121	21	0.00086 557	3.421	0.2	0.00170 8	V\$P AX_ Q6= =>hs a- miR- 19b in clust er clust	

									er29 2_hs a- mir- 106a	
hsa- miR- 19b	520	V\$ATF 4_Q2	32	9	0.00086 616	5.1012	0.2	0.00170 8		
hsa- miR- 29a	540	V\$ZIC2 01	71	15	0.00086 69	4.0098	0.2	0.00170 8		
hsa- miR- 93	541	V\$SPZ 1_01	37	10	0.00087 084	4.1536	0.2	0.00170 8		TFs unmapped
hsa- miR- 138	394	V\$RP5 8_01	96	15	0.00087 291	3.8723	0.2	0.00170 8		
hsa- miR- 217	171	V\$ELK 1_02	42	6	0.00088 153	4.27	0.2	0.00170 8		
hsa- miR- 138	394	V\$GAT A3_01	8	4	0.00088 251	4.6873	0.2	0.00170 8		
hsa- miR- 199b	190	V\$MY OD_Q6 01	38	6	0.00088 631	4.2419	0.2	0.00170 8		
hsa- miR- 29c	547	V\$TCF 11MAF G_01	164	27	0.00088 744	3.5072	0.2	0.00170 8		
hsa- miR- 185	267	V\$P53_ 01	85	11	0.00088 837	3.5672	0.2	0.00170 8		
hsa- miR- 215	75	V\$IRF_ Q6	170	8	0.00089 764	4.2767	0.2	0.00170 8		
hsa- miR- 29b	542	V\$ZIC2 01	71	15	0.00090 077	3.7732	0.2	0.00170 8		
hsa- miR- 19a	523	V\$ATF 4_Q2	32	9	0.00090 302	4.5372	0.2	0.00170 8		
hsa- miR- 210	15	V\$YY1 01	83	3	0.00091 118	6.4754	0.2	0.00170 8		
hsa- miR- 320	382	V\$CRE B_Q2_0 1	164	21	0.00091 562	3.0719	0.2	0.00170 8		
hsa- miR- 136	128	V\$EVI1 06	124	9	0.00092 114	4.1542	0.2	0.00170 8	V\$E VI1_ 04= =>hs a- miR- 136 in clust er clust er77	TFs unmapped

									hsa-mir-493	
hsa-miR-199b	190	V\$S8_01	138	12	0.00092525	2.9862	0.2	0.001708		TFs unmapped
hsa-miR-19a	523	V\$PAX6_Q2	121	21	0.00093246	3.5636	0.2	0.001708		
hsa-miR-150	181	V\$MYB_Q5_01	16	4	0.00093628	4.4512	0.2	0.001708		hsa-miR-150==> TF cluster 312: V\$CMYB_01, V\$MYB_Q3, V\$MYB_Q5_01, V\$MYB_Q6, (NM_005375)
hsa-miR-129	204	V\$CEBPB_01	49	7	0.00094407	4.0583	0.2	0.001708		
hsa-miR-126-star	274	V\$AP4_01	37	7	0.0009464	4.7974	0.2	0.001708		
hsa-miR-34b	246	V\$AP1_Q4	41	7	0.00094953	3.8092	0.2	0.001708		TFs unmapped
hsa-miR-20a	571	V\$GATA1_05	166	28	0.00095002	3.2308	0.2	0.001708		
hsa-miR-130a	488	V\$CDC5_01	222	31	0.00095264	2.9302	0.2	0.001708		
hsa-miR-10b	131	V\$AIRE_02	201	12	0.00095639	4.1105	0.2	0.001708		
hsa-miR-10a	131	V\$AIRE_02	201	12	0.00095639	4.1956	0.2	0.001708	V\$AIRE_02==>hsa-miR-10a in cluster11_hsa-mir-10a	
hsa-	429	V\$FOX	137	20	0.00096	2.8021	0.2	0.00170		

miR-101		J2_01			251			8		
hsa-miR-16	577	V\$OCT1_03	54	13	0.00096385	3.556	0.2	0.001708		
hsa-miR-214	412	V\$OCT_C	297	34	0.0009644	2.9446	0.2	0.001708		
hsa-miR-142-5p	284	V\$E12_Q6	18	5	0.00097512	3.5508	0.2	0.001708		
hsa-miR-149	208	V\$PR_Q2	24	5	0.00097815	4.3067	0.2	0.001708		
hsa-miR-34b	246	V\$EVI1_01	170	16	0.00098273	3.6	0.2	0.001708	V\$EVI1_03=>hsa-miR-34b in cluster cluster47_hsa-mir-34b	TFs unmapped
hsa-miR-30b	624	V\$FREAC7_01	175	31	0.00098551	2.4777	0.2	0.001708		
hsa-miR-9-star	300	V\$FOX P1_01	195	20	0.00098552	2.958	0.2	0.001708	V\$FOX P1_01=>hsa-miR-9-star in cluster cluster209_hsa-mir-9-2	TFs unmapped
hsa-miR-28	124	V\$NRF2_Q4	156	10	0.00098603	4.7769	0.2	0.001708		
hsa-miR-302d	346	V\$TAX CREB_01	88	13	0.00098785	3.4612	0.2	0.001708		
hsa-miR-129	204	V\$RFX_Q6	79	9	0.00098871	4.1245	0.2	0.001708		

hsa-miR-29c	547	V\$ZIC2_01	71	15	0.00099045	3.6629	0.2	0.001708		
hsa-miR-368	110	V\$FREAC4_01	208	11	0.00099489	3.9621	0.2	0.001708		
hsa-miR-205	242	V\$MYOGNF1_01	67	9	0.0009988	4.01	0.2	0.001708		
hsa-miR-219	173	V\$PPARG_01	93	9	0.00099889	3.763	0.2	0.001708	V\$PPARG_02==>hsa-miR-219 in cluster cluster20_hsa-mir-219-1	TFs unmapped
hsa-miR-301	468	V\$CDC5_01	222	30	0.0010003	3.1303	0.2	0.001708		
hsa-miR-103	580	V\$OCT1_03	54	13	0.0010119	3.7415	0.2	0.001708		
hsa-miR-146a	110	V\$STAT5A_01	91	7	0.0010261	4.3032	0.2	0.001708		
hsa-miR-367	346	V\$CORBININDINGFACTOR_Q6	170	20	0.0010312	3.1473	0.2	0.001708		TFs unmapped
hsa-miR-346	81	V\$MYB_Q5_01	16	3	0.0010347	5.7931	0.2	0.001708		
hsa-miR-339	155	V\$CREBP1CJUN_01	65	7	0.0010391	4.6466	0.2	0.001708		
hsa-miR-222	208	V\$TCF11MAFG_01	164	14	0.0010409	3.7146	0.2	0.001708		
hsa-miR-23a	391	V\$POU6F1_01	302	33	0.0010417	2.4972	0.2	0.001708		TFs unmapped
hsa-miR-206	400	V\$ATFB	137	19	0.0010424	2.9574	0.2	0.001708		TFs unmapped
hsa-miR-187	15	V\$TCF1P_Q6	87	3	0.0010451	5.7075	0.2	0.001708		TFs unmapped

hsa-miR-27b	590	V\$HNF 1_C	154	27	0.00104 52	3.0209	0.2	0.00170 8		
hsa-miR-369-3p	328	V\$NKX 25_02	331	31	0.00104 66	2.6679	0.2	0.00170 8		TFs unmapped
hsa-miR-16	577	V\$CDP CR1_01	89	18	0.00105 08	3.3513	0.2	0.00170 8	V\$CDP_02= =>hsa-miR-16 in cluster188_hsa-mir-15b	
hsa-miR-137	360	V\$SOX Q6	152	19	0.00105 39	3.5394	0.2	0.00170 8		
hsa-miR-133b	333	V\$ZID_01	92	13	0.00106 01	3.867	0.2	0.00170 8		
hsa-miR-191	28	V\$OCT1_B	180	5	0.00106 63	4.1691	0.2	0.00170 8		
hsa-miR-23a	391	V\$RFX Q6	79	13	0.00108 61	3.5127	0.2	0.00170 8	V\$RFX1_02= =>hsa-miR-23a in cluster129_hsa-mir-23a	
hsa-miR-190	91	V\$HNF1_01	179	9	0.00108 78	4.082	0.2	0.00170 8		
hsa-miR-15a	585	V\$OCT1_03	54	13	0.00109 64	3.2875	0.2	0.00170 8		
hsa-miR-195	585	V\$OCT1_03	54	13	0.00109 64	3.2971	0.2	0.00170 8	V\$OCT1_01= =>hsa-miR-	

									195 in clust er clust er10 2_hs a- mir- 497	
hsa-miR-375	160	V\$HMG GIY_Q 3	123	10	0.00112 5	3.9979	0.2	0.00170 8		
hsa-miR-192	79	V\$MY CMAX 03	37	4	0.00113 04	4.5696	0.2	0.00170 8		
hsa-miR-19a	523	V\$POU 6F1_01	302	41	0.00113 4	2.5806	0.2	0.00170 8		TFs unmapped
hsa-miR-30b	624	V\$FAC 1_01	207	35	0.00113 75	2.4242	0.2	0.00170 8		
hsa-miR-372	560	V\$SPZ 1_01	37	10	0.00113 94	3.7025	0.2	0.00170 8		TFs unmapped
hsa-miR-28	124	V\$FRE AC2_01	217	12	0.00114 92	3.4885	0.2	0.00170 8		
hsa-miR-369-3p	328	V\$STA T5A_02	155	18	0.00115 45	2.8878	0.2	0.00170 8		
hsa-miR-219	173	V\$ISRE 01	177	13	0.00115 49	3.4166	0.2	0.00170 8		TFs unmapped
hsa-miR-129	204	V\$FOX M1_01	132	12	0.00116 39	3.5537	0.2	0.00170 8		TFs unmapped
hsa-miR-124a	571	V\$NFK APPAB 65_01	49	12	0.00116 51	3.3979	0.2	0.00170 8		
hsa-miR-182	501	V\$YY1 Q6	137	22	0.00116 83	3.2459	0.2	0.00170 8		
hsa-miR-140	180	V\$E2F1 DP2_01	17	4	0.00117 25	4.2904	0.2	0.00170 8		TFs unmapped
hsa-miR-372	560	V\$P53_01	85	17	0.00117 41	3.2434	0.2	0.00170 8		
hsa-let-7g	503	V\$AP1 Q4	41	10	0.00117 56	3.5175	0.2	0.00170 8		TFs unmapped
hsa-miR-155	178	V\$OCT 1_07	262	17	0.00117 67	3.3348	0.2	0.00170 8		
hsa-miR-210	15	V\$E2F_01	91	3	0.00119 09	5.444	0.2	0.00170 8		

hsa-miR-23b	395	V\$RFX_Q6	79	13	0.0011928	3.3101	0.2	0.001708		
hsa-miR-328	207	V\$STA_T1_01	37	6	0.0011978	4.1743	0.2	0.001708		
hsa-miR-25	312	V\$FOX_J2_01	137	16	0.0012011	3.6483	0.2	0.001708		
hsa-miR-339	155	V\$ARP_1_01	86	8	0.0012172	4.0341	0.2	0.001708		
hsa-miR-368	110	V\$HLF_01	181	10	0.0012202	4.8468	0.2	0.001708		TFs unmapped
hsa-miR-15b	592	V\$OCT_1_03	54	13	0.0012247	3.6659	0.2	0.001708		
hsa-miR-335	136	V\$CRE_B_Q2	98	8	0.001227	3.4835	0.2	0.001708		
hsa-miR-126-star	274	V\$EVI1_04	156	16	0.0012275	3.1735	0.2	0.001708		TFs unmapped
hsa-miR-15a	585	V\$CDP_CR1_01	89	18	0.0012323	3.3848	0.2	0.001708		
hsa-miR-195	585	V\$CDP_CR1_01	89	18	0.0012323	3.6658	0.2	0.001708		
hsa-miR-375	160	V\$FRE_AC2_01	217	14	0.0012334	3.6782	0.2	0.001708		
hsa-miR-155	178	V\$FOX_P1_01	195	14	0.0012355	3.7455	0.2	0.001708		TFs unmapped
hsa-miR-302c	312	V\$PR_02	76	11	0.0012356	3.3651	0.2	0.001708		TFs unmapped
hsa-miR-101	429	V\$PIT1_Q6	120	18	0.0012423	3.0695	0.2	0.001708		
hsa-miR-184	16	V\$TAL1ALPH_AE47_01	21	2	0.00125	8.2688	0.2	0.001708		
hsa-miR-92	413	V\$MY_OGNF1_01	67	12	0.0012515	3.5547	0.2	0.001708		
hsa-miR-369-3p	328	V\$IRF7_01	182	20	0.0012523	3.1043	0.2	0.001708		
hsa-miR-30e-5p	629	V\$CDC_5_01	222	37	0.0012629	2.3714	0.2	0.001708		
hsa-	236	V\$AHR	100	11	0.00126	3.0784	0.2	0.00170		

miR-139		ARNT_01			41			8		
hsa-miR-183	219	V\$E2F_Q3	62	8	0.0013076	3.747	0.2	0.001708		TFs unmapped
hsa-miR-185	267	V\$CDP CR1_01	89	11	0.0013078	3.597	0.2	0.001708		
hsa-miR-215	75	V\$CREB_Q4	102	6	0.0013093	4.5426	0.2	0.001708		
hsa-miR-134	88	V\$MYB_Q5_01	16	3	0.0013163	4.5608	0.2	0.001708		
hsa-miR-184	16	V\$PPARA_01	88	3	0.0013163	5.0244	0.2	0.001708		
hsa-miR-320	382	V\$CREL_01	45	9	0.0013253	3.7164	0.2	0.001708		
hsa-miR-143	174	V\$POU3F2_01	201	14	0.0013283	3.2912	0.2	0.001708		
hsa-miR-142-Sp	284	V\$HLF_01	181	18	0.001341	2.6577	0.2	0.001708		TFs unmapped
hsa-miR-155	178	V\$FREAC7_01	175	13	0.0013516	3.2248	0.2	0.001708		
hsa-miR-143	174	V\$MEF2_03	78	8	0.0013528	3.7133	0.2	0.001708		
hsa-miR-302b	314	V\$TAX CREB_01	88	12	0.0013561	3.2848	0.2	0.001708		
hsa-miR-368	110	V\$LMO2COM_02	123	8	0.0013574	3.4019	0.2	0.001708		
hsa-miR-182	501	V\$HIF1_Q5	49	11	0.0013669	3.1824	0.2	0.001708		
hsa-miR-184	16	V\$AREB6_01	22	2	0.0013729	7.0851	0.2	0.001708		TFs unmapped
hsa-miR-132	191	V\$AP1_Q4	41	6	0.0013754	3.2858	0.2	0.001708	V\$AP1_01, V\$AP1_Q4 ==> hsa-miR-132 in cluster10	TFs unmapped

									1_hs a- mir- 212	
hsa- miR- 212	191	V\$AP1 _Q4	41	6	0.00137 54	3.3562	0.2	0.00170 8	V\$A P1_0 1,V\$ AP1 _Q4 => hsa- miR- 212 in clust er clust er10 1_hs a- mir- 212	TFs unmapped
hsa- miR- 142- 5p	284	V\$MY OD_Q6 _01	38	7	0.00137 79	4.081	0.2	0.00170 8		
hsa- miR- 15b	592	V\$CDX 2_Q5	270	41	0.00138 38	2.5989	0.2	0.00170 8		TFs unmapped
hsa- miR- 182	501	V\$SOX 5_01	96	17	0.00140 07	3.0415	0.2	0.00170 8	V\$S OX_ Q6= =>hs a- miR- 182 in clust er clust er24 2_hs a- mir- 183	hsa-miR- 182=> TF cluster 280: V\$SOX5_ 01, V\$SOX_ Q6, (NM_006 940)
hsa- miR- 302a	342	V\$ATF 4_Q2	32	7	0.00140 17	4.7091	0.2	0.00170 8		
hsa- miR- 29a	540	V\$PAX 6_Q2	121	21	0.00140 27	3.0241	0.2	0.00170 8		
hsa- miR- 10a	131	V\$PR_ Q2	24	4	0.00140 54	3.9132	0.2	0.00170 8		
hsa- miR- 21	135	V\$HNF 4_01_B	58	6	0.00145	4.1413	0.2	0.00170 8		
hsa- miR-	110	V\$ZIC2 _01	71	6	0.00145 38	3.782	0.2	0.00170 8		

368										
hsa-miR-130a	488	V\$SOX_Q6	152	23	0.0014578	2.838	0.2	0.001708		hsa-miR-130a==> TF cluster 279: V\$SOX_Q6, hsa-miR-130a==> TF cluster 280: V\$SOX5_01, V\$SOX_Q6, (NM_003107 NM_006940 NM_007084)
hsa-miR-30e-3p	226	V\$NFA_T_Q4_01	7	3	0.0014586	4.3425	0.2	0.001708		
hsa-miR-125b	370	V\$CREB_01	47	9	0.0014639	3.2506	0.2	0.001708		
hsa-miR-29b	542	V\$PAX6_Q2	121	21	0.0014696	3.0737	0.2	0.001708		
hsa-miR-103	580	V\$PAX6_Q2	121	22	0.0014753	3.4437	0.2	0.001708		
hsa-miR-302a	342	V\$SOX_Q6	152	18	0.0014811	3.3065	0.2	0.001708		
hsa-miR-20b	563	V\$MYOD_Q6_01	38	10	0.0014845	3.6394	0.2	0.001708		
hsa-miR-302d	346	V\$ATF4_Q2	32	7	0.0014999	4.4942	0.2	0.001708		
hsa-miR-138	394	V\$E2F_01	91	14	0.0015012	3.2541	0.2	0.001708		
hsa-miR-148a	321	V\$HFH4_01	149	17	0.0015127	2.9751	0.2	0.001708		
hsa-miR-326	261	V\$TAL1BETA E47_01	31	6	0.0015131	4.0273	0.2	0.001708		TFs unmapped
hsa-miR-15a	585	V\$FREAC7_01	175	29	0.0015148	2.787	0.2	0.001708		
hsa-miR-331	205	V\$HNF1_C	154	13	0.0015208	3.0954	0.2	0.001708		
hsa-	88	V\$E2F	36	4	0.00152	4.3649	0.2	0.00170		TFs

miR-134		Q4			27			8		unmapped
hsa-miR-129	204	V\$MZF1_02	68	8	0.0015259	3.6883	0.2	0.001708		
hsa-miR-326	261	V\$OCT1_06	107	12	0.0015498	3.0782	0.2	0.001708	V\$OCT_C=>hsa-miR-326 in cluster cluster46_hsa-mir-326	
hsa-miR-93	541	V\$E2F_Q3_01	7	4	0.0015613	6.3707	0.2	0.001708	V\$E2F_Q3_01, V\$E2F_Q4, V\$E2F_Q4_01, V\$E2F_Q6, V\$E2F_Q6_01, V\$E2F_Q1, V\$E2F_Q2, V\$E2F_Q3, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-93=> TF cluster 58: V\$E2F_Q3_01, V\$E2F_Q4, V\$E2F_Q4_01, V\$E2F_Q6, V\$E2F_Q6_01, V\$E2F_Q1, V\$E2F_Q2, V\$E2F_Q3, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-93=> TF cluster 62: V\$E2F_Q4_01, V\$E2F_Q2, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949	

										NM_0052 25)
hsa-miR-134	88	V\$AM L_Q6	61	5	0.00156 76	4.0085	0.2	0.00170 8		
hsa-miR-96	544	V\$ETS Q4	16	6	0.00157 09	3.2428	0.2	0.00170 8		
hsa-miR-181a	476	V\$FOX P1_01	195	27	0.00157 62	3.0517	0.2	0.00170 8		TFs unmapped
hsa-miR-181c	476	V\$FOX P1_01	195	27	0.00157 62	3.4414	0.2	0.00170 8		TFs unmapped
hsa-miR-145	230	V\$SRE BP_Q3	75	9	0.00158 03	3.9169	0.2	0.00170 8		
hsa-miR-302c -star	343	V\$OCT C	297	29	0.00158 67	2.6684	0.2	0.00170 8	V\$O CT1 _06= =>hs a- miR- 302c -star in clust er clust er20 1_hs a- mir- 302b	
hsa-miR-93	541	V\$CRE B_Q2	98	18	0.00159 58	2.8204	0.2	0.00170 8		
hsa-miR-125a	375	V\$CRE B_01	47	9	0.00160 81	3.0196	0.2	0.00170 8		
hsa-miR-183	219	V\$MEF 2_04	163	14	0.00161 03	3.158	0.2	0.00170 8		
hsa-miR-25	312	V\$PAX 3_01	115	14	0.00161 22	3.6978	0.2	0.00170 8		
hsa-miR-152	323	V\$HFH 4_01	149	17	0.00161 79	2.9994	0.2	0.00170 8		
hsa-miR-191	28	V\$LHX 3_01	116	4	0.00162 45	4.6921	0.2	0.00170 8		
hsa-miR-181b	477	V\$FOX P1_01	195	27	0.00162 54	2.697	0.2	0.00170 8		TFs unmapped
hsa-miR-	352	V\$HFH 4_01	149	18	0.00163	3.3089	0.2	0.00170 8		

34c										
hsa-miR-196a	136	V\$MM EF2_Q6	152	10	0.00163 9	3.6515	0.2	0.00170 8	V\$ MEF 2_03 => hsa- miR- 196a in clust er clust er53 _hsa- mir- 196a- 2	
hsa-miR-183	219	V\$CEB P_C	128	12	0.00163 97	3.6681	0.2	0.00170 8		
hsa-miR-29c	547	V\$PAX 6_Q2	121	21	0.00164 88	3.0015	0.2	0.00170 8		
hsa-miR-24	291	V\$OCT 1_B	180	18	0.00165 72	3.0005	0.2	0.00170 8		
hsa-miR-26a	465	V\$PBX 1_01	87	15	0.00165 96	3.3877	0.2	0.00170 8	V\$P BX_ Q3= =>hs a- miR- 26a in clust er clust er57 _hsa- mir- 26a- 2	TFs unmapped
hsa-miR-182	501	V\$FOX O4_01	36	9	0.00166 15	4.1652	0.2	0.00170 8		
hsa-miR-328	207	V\$MZF 1_02	68	8	0.00167 47	3.9119	0.2	0.00170 8		
hsa-miR-326	261	V\$HSF _Q6	108	12	0.00168 03	3.4909	0.2	0.00170 8		TFs unmapped
hsa-miR-302d	346	V\$SOX _Q6	152	18	0.00168 79	3.2921	0.2	0.00170 8		
hsa-miR-142-5p	284	V\$IRF_ Q6	170	17	0.00170 8	2.6761	0.2	0.00170 8		
hsa-	106	V\$MY	31	4	0.00171	4.4451	0.3	0.00520		

miR-146b		B_Q3			78			27		
									V\$F OXJ 2_01 ,V\$F OXJ 2_02 => hsa-miR-129 in clust er clust er40 _hsa- mir-129- 2 V\$F OXJ 2_02 => hsa-miR-129 in clust er clust er24 1_hs a-mir-129-1	
hsa-miR-129	204	V\$FOX J2_02	300	20	0.00171 8	3.3104	0.3	0.00520 27		
hsa-miR-215	75	V\$SEF 1_C	73	5	0.00171 82	3.8087	0.3	0.00520 27		TFs unmapped
hsa-miR-25	312	V\$OLF 1_01	46	8	0.00172 51	4.3291	0.3	0.00520 27		TFs unmapped
hsa-miR-33	264	V\$CAR T1_01	335	26	0.00174 89	3.1306	0.3	0.00520 27		
hsa-miR-33	264	V\$FOX J2_02	300	24	0.00174 97	2.7438	0.3	0.00520 27		
hsa-miR-155	178	V\$HOX 13_01	62	7	0.00175 33	3.8089	0.3	0.00520 27		TFs unmapped
hsa-miR-339	155	V\$FAC 1_01	207	13	0.00176 04	3.5781	0.3	0.00520 27		
hsa-miR-107	588	V\$PAX 6_Q2	121	22	0.00176 08	2.8891	0.3	0.00520 27		

hsa-miR-320	382	V\$CHX 10_01	196	23	0.00176 7	2.6106	0.3	0.00520 27		
hsa-miR-22	265	V\$CM YB_01	54	8	0.00177 27	4.2956	0.3	0.00520 27	V\$ MY B_Q 3== >hsa - miR- 22 in clust er clust er10 0_hs a- mir- 22	
hsa-miR-372	560	V\$E2F_ Q3_01	7	4	0.00177 92	5.7473	0.3	0.00520 27	hsa-miR-372==> TF cluster 58: V\$E2F1_ Q3_01, V\$E2F1_ Q4, V\$E2F1_ Q4_01, V\$E2F1_ Q6, V\$E2F1_ Q6_01, V\$E2F_0 1, V\$E2F_0 2, V\$E2F_0 3, V\$E2F_Q 3_01, V\$E2F_Q 4_01, V\$E2F_Q 6_01, hsa- miR- 372==> TF cluster 62: V\$E2F1_ Q4_01, V\$E2F_0 2, V\$E2F_Q 3_01, V\$E2F_Q 4_01, V\$E2F_Q 6_01, (NM_001	

										949 NM_005225)
hsa-miR-198	250	V\$YY1_02	161	15	0.0018308	2.9205	0.3	0.0052027		
hsa-miR-368	110	V\$NKX25_02	331	14	0.0018334	3.6229	0.3	0.0052027		TFs unmapped
hsa-miR-19a	523	V\$FOXJ2_02	300	40	0.0018351	2.7296	0.3	0.0052027		
hsa-miR-199b	190	V\$SREBP_Q3	75	8	0.0018372	3.7425	0.3	0.0052027		
hsa-miR-210	15	V\$FOXO1_02	106	3	0.0018507	5.2263	0.3	0.0052027		
hsa-miR-218	417	V\$S8_01	138	19	0.0018561	3.0214	0.3	0.0052027	V\$S8_01 => hsa-miR-218 in cluster cluster216_hsa-mir-218-2	TFs unmapped
hsa-miR-204	299	V\$AMEF2_Q6	206	20	0.0018569	3.0993	0.3	0.0052027	V\$MEF2_01 => hsa-miR-204 in cluster cluster266_hsa-mir-204	
hsa-miR-372	560	V\$SRYO2	81	16	0.0018603	3.0607	0.3	0.0052027		
hsa-miR-134	88	V\$OCT1_04	93	6	0.0018609	3.5209	0.3	0.0052027		
hsa-miR-	441	V\$GATA1_04	121	18	0.0018684	2.8821	0.3	0.0052027		

200c										
hsa-miR-19b	520	V\$POU6F1_01	302	40	0.0018686	2.5878	0.3	0.0052027	V\$POU6F1_01==>hsa-miR-19b in cluster292_hsa-mir-106a	TFs unmapped
hsa-miR-30a-5p	625	V\$CDP_01	197	33	0.0018797	2.6133	0.3	0.0052027		
hsa-miR-92	413	V\$TST1_01	150	20	0.0018797	3.2522	0.3	0.0052027	V\$TST1_01==>hsa-miR-92 in cluster292_hsa-mir-106a	
hsa-miR-26b	471	V\$PBX1_01	87	15	0.0018849	3.3102	0.3	0.0052027		TFs unmapped
hsa-miR-214	412	V\$ARN_T_02	109	16	0.0018947	2.842	0.3	0.0052027		
hsa-miR-222	208	V\$P53_01	85	9	0.0019117	3.4789	0.3	0.0052027		
hsa-miR-190	91	V\$E2F_03	37	4	0.0019117	4.6692	0.3	0.0052027		
hsa-miR-206	400	V\$OCT1_03	54	10	0.0019131	3.3125	0.3	0.0052027		
hsa-miR-323	246	V\$TGIF_01	101	11	0.001914	3.7093	0.3	0.0052027	hsa-miR-323==>TF cluster291: V\$TGIF_01, (NM_003	

										244)
hsa-miR-369-3p	328	V\$EGR_3_01	35	7	0.0019147	3.3875	0.3	0.0052027		
hsa-miR-32	444	V\$TST_1_01	150	21	0.0019292	2.8198	0.3	0.0052027		
hsa-miR-215	75	V\$MAF_Q6	75	5	0.0019381	3.4953	0.3	0.0052027		TFs unmapped
hsa-miR-122a	116	V\$E47_02	14	3	0.0019434	5.9248	0.3	0.0052027		TFs unmapped
hsa-miR-30c	624	V\$PBX_1_01	87	18	0.0019574	3.0173	0.3	0.0052027		TFs unmapped
hsa-miR-211	304	V\$YY1_02	161	17	0.0019634	2.8618	0.3	0.0052027		
hsa-miR-134	88	V\$DR4_Q2	94	6	0.0019657	3.5446	0.3	0.0052027		
hsa-miR-146a	110	V\$MYB_Q3	31	4	0.001969	4.7794	0.3	0.0052027		
hsa-miR-29a	540	V\$FREAC7_01	175	27	0.0019759	2.7714	0.3	0.0052027		
hsa-miR-190	91	V\$FOX_P1_01	195	9	0.0019776	3.7488	0.3	0.0052027		TFs unmapped
hsa-miR-368	110	V\$OCT_C	297	13	0.0019826	3.373	0.3	0.0052027		
hsa-miR-1	402	V\$OCT_1_03	54	10	0.0019856	3.2242	0.3	0.0052027	V\$OCT1_B=>hsa-miR-1 in cluster cluster12_2_hsa-mir-1-2	
hsa-miR-30a-5p	625	V\$PBX_1_01	87	18	0.0019929	2.904	0.3	0.0052027		TFs unmapped
hsa-miR-326	261	V\$PR_01	82	10	0.0020136	3.5999	0.3	0.0052027		TFs unmapped
hsa-miR-	151	V\$MYOD_Q6	38	5	0.0020164	3.8382	0.3	0.0052027		

199a		_01								
hsa-miR-320	382	V\$CDC 5_01	222	25	0.00202 45	2.3114	0.3	0.00520 27		
hsa-miR-139	236	V\$FOX O4_01	36	6	0.00202 63	5.0035	0.3	0.00520 27		
hsa-miR-186	415	V\$E2F_ Q4_	36	8	0.00202 72	3.0851	0.3	0.00520 27		TFs unmapped
hsa-miR-342	143	V\$TGI F_01	101	8	0.00205 41	3.5151	0.3	0.00520 27		hsa-miR-342==> TF cluster 291: V\$TGIF_ 01, (NM_003 244)
hsa-miR-138	394	V\$DR4 _Q2	94	14	0.00206 15	3.5207	0.3	0.00520 27		hsa-miR-138==> TF cluster 248: V\$DR4_ Q2, hsa- miR- 138==> TF cluster 259: V\$DR3_ Q4, V\$DR4_ Q2, V\$PPAR A_02, (NM_000 964 NM_0029 57)
hsa-miR-302a	342	V\$P53_ 01	85	12	0.00206 92	3.3715	0.3	0.00520 27		
hsa-miR-101	429	V\$NRF 2_Q4	156	21	0.00207 05	2.7525	0.3	0.00520 27		hsa-miR-101==> TF cluster 214: V\$MAF_ Q6_01, V\$NRF2_ Q4, (NM_006 164)
hsa-miR-199a	151	V\$SRE BP_Q3	75	7	0.00207 77	3.003	0.3	0.00520 27		
hsa-miR-9-star	300	V\$TCF 11MAF G_01	164	17	0.00208 1	2.9416	0.3	0.00520 27		
hsa-	333	V\$ALX	148	17	0.00208	3.044	0.3	0.00520		

miR-133b		4_01			47			27		
hsa-miR-96	544	V\$ZID_01	92	17	0.0021141	3.1244	0.3	0.0052027		
hsa-miR-181c	476	V\$ROR A2_01	229	30	0.0021489	2.8677	0.3	0.0052027		
hsa-miR-181a	476	V\$ROR A2_01	229	30	0.0021489	2.9718	0.3	0.0052027		
hsa-miR-30e-3p	226	V\$MEF 2_04	163	14	0.0021653	3.358	0.3	0.0052027	V\$H MEF 2_Q 6==>hsa-miR-30e-3p in cluster5_hsa-mir-30e	
hsa-miR-30a-3p	226	V\$MEF 2_04	163	14	0.0021653	3.6864	0.3	0.0052027		
hsa-miR-372	560	V\$IRF_Q6	170	27	0.0021745	2.7418	0.3	0.0052027	hsa-miR-372==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-372==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_01, (NM_002198 NM_002199)	
hsa-miR-199b	190	V\$E47_01	31	5	0.0021822	3.8487	0.3	0.0052027	TFs unmapped	
hsa-	274	V\$CM	54	8	0.00218	3.6937	0.3	0.00520		

miR-126-star		YB_01			91			27		
hsa-miR-27a	582	V\$CREL_01	45	11	0.0021965	3.0465	0.3	0.0052027		
hsa-miR-96	544	V\$FREAC7_01	175	27	0.0021979	2.614	0.3	0.0052027		
hsa-miR-331	205	V\$ROAZ_01	123	11	0.0022021	3.3534	0.3	0.0052027		TFs unmapped
hsa-miR-331	205	V\$PPARA_01	88	9	0.0022053	3.8116	0.3	0.0052027		
hsa-miR-133a	318	V\$ZID_01	92	12	0.0022268	3.3907	0.3	0.0052027		
hsa-miR-222	208	V\$SRF_Q6	87	9	0.0022493	3.1038	0.3	0.0052027	V\$SRF_01,V\$SRF_Q6==>hsa-miR-222 in cluster cluster280_hsa-miR-222	
hsa-miR-302a-star	38	V\$CEBPGAMMA_Q6	155	5	0.0022618	3.8114	0.3	0.0052027		
hsa-miR-219	173	V\$EFC_Q6	85	8	0.0022719	3.4781	0.3	0.0052027		
hsa-miR-182	501	V\$HIF1_Q3	52	11	0.0022765	3.3296	0.3	0.0052027		
hsa-miR-302d	346	V\$P53_01	85	12	0.0022812	3.1788	0.3	0.0052027		
hsa-miR-328	207	V\$ERR1_Q2	56	7	0.0022848	3.9833	0.3	0.0052027	hsa-miR-328==>TF cluster 73: V\$ERR1_Q2, (NM_004451)	

hsa-miR-302a	342	V\$PAX6_Q2	121	15	0.002298	2.916	0.3	0.0052027	V\$PAX6_Q1= =>hsa-miR-302a in cluster201_hsa-mir-302b	
hsa-miR-152	323	V\$CDC5_01	222	22	0.0022986	2.6959	0.3	0.0052027		
hsa-miR-33	264	V\$EGR2_01	23	5	0.0023103	4.3498	0.3	0.0052027		
hsa-miR-136	128	V\$HSF1_01	46	5	0.0023129	4.1183	0.3	0.0052027		
hsa-miR-32	444	V\$MYOGNF1_01	67	12	0.0023219	3.6293	0.3	0.0052027		
hsa-miR-144	428	V\$CEBPB_02	117	17	0.0023312	2.7453	0.3	0.0052027		
hsa-miR-208	59	V\$CDP_01	197	7	0.0023395	3.7005	0.3	0.0052027		
hsa-miR-302c	312	V\$DEC_Q1	59	9	0.0023411	3.6249	0.3	0.0052027		
hsa-miR-338	203	V\$COMP1_01	73	8	0.002342	3.5168	0.3	0.0052027		TFs unmapped
hsa-miR-368	110	V\$GATA1_02	134	8	0.0023422	3.8568	0.3	0.0052027		
hsa-miR-302c-star	343	V\$ARN_T_02	109	14	0.002343	2.8607	0.3	0.0052027		
hsa-miR-371	19	V\$STR_A13_01	90	3	0.0023562	5.7355	0.3	0.0052027		TFs unmapped
hsa-miR-340	8	V\$DEC_Q1	59	2	0.0023571	6.445	0.3	0.0052027		
hsa-miR-190	91	V\$NKX22_01	127	7	0.0023608	4.0263	0.3	0.0052027		
hsa-miR-29c	547	V\$FREAC7_01	175	27	0.0023782	2.766	0.3	0.0052027		

hsa-miR-133a	318	V\$NFY_Q6_01	28	6	0.002385	3.2755	0.3	0.0052027		
hsa-miR-210	15	V\$LHX_3_01	116	3	0.0023966	4.9954	0.3	0.0052027		
hsa-miR-194	186	V\$FOX_J2_01	137	11	0.0024097	2.9678	0.3	0.0052027		
hsa-miR-190	91	V\$AIR_E_02	201	9	0.002433	3.9391	0.3	0.0052027		
hsa-miR-320	382	V\$CEB_PA_01	40	8	0.0024413	3.4486	0.3	0.0052027		
hsa-miR-133a	318	V\$OCT_1_04	93	12	0.0024432	3.2997	0.3	0.0052027	V\$OCT1_B=>hsa-miR-133a in cluster cluster12_2_hsa-mir-1-2	
hsa-miR-7	252	V\$ELF_1_Q6	73	9	0.002447	4.0702	0.3	0.0052027		
hsa-miR-144	428	V\$FOX_O4_01	36	8	0.0024641	3.7657	0.3	0.0052027		
hsa-miR-138	394	V\$AIR_E_01	66	11	0.0024728	3.2227	0.3	0.0052027		
hsa-miR-223	139	V\$IK3_01	107	8	0.0024758	3.4822	0.3	0.0052027		TFs unmapped
hsa-miR-299-3p	59	V\$TGI_F_01	101	5	0.0024841	4.4421	0.3	0.0052027		
hsa-miR-219	173	V\$EVI1_01	170	12	0.0024922	2.7231	0.3	0.0052027		TFs unmapped
hsa-miR-144	428	V\$S8_01	138	19	0.0025002	2.6345	0.3	0.0052027		TFs unmapped
hsa-miR-146a	110	V\$MYB_Q5_01	16	3	0.0025013	4.4088	0.3	0.0052027		
hsa-miR-141	315	V\$OCT_1_01	159	17	0.0025018	2.6007	0.3	0.0052027		

hsa-miR-371	19	V\$ZID_01	92	3	0.002509	4.8916	0.3	0.0052027		
hsa-miR-155	178	V\$HNF3ALPHA_Q6	84	8	0.0025184	3.2402	0.3	0.0052027		
hsa-miR-323	246	V\$NKX25_02	331	24	0.0025223	3.1267	0.3	0.0052027		TFs unmapped
hsa-miR-205	242	V\$CEBPB_01	49	7	0.0025323	4.0139	0.3	0.0052027	V\$CEBPB_01,V\$CEBP_Q3==>hsa-miR-205 in cluster cluster22_hsa-mir-205	
hsa-miR-9-star	300	V\$CHX10_01	196	19	0.0025352	2.6694	0.3	0.0052027		
hsa-miR-153	359	V\$GCNF_01	140	17	0.002537	3.1483	0.3	0.0052027		
hsa-miR-34c	352	V\$STAT5A_02	155	18	0.0025429	3.2721	0.3	0.0052027		
hsa-miR-218	417	V\$GATA1_04	121	17	0.0025505	3.0267	0.3	0.0052027		
hsa-miR-101	429	V\$POU6F1_01	302	34	0.002551	2.1323	0.3	0.0052027		TFs unmapped
hsa-miR-184	16	V\$E2F1_Q4_01	1	1	0.0025555	12.4162	0.3	0.0052027		
hsa-miR-10b	131	V\$OLF1_01	46	5	0.0025595	4.0191	0.3	0.0052027		TFs unmapped
hsa-miR-10a	131	V\$OLF1_01	46	5	0.0025595	4.1311	0.3	0.0052027		TFs unmapped
hsa-miR-206	400	V\$IRF_Q6	170	21	0.0025662	3.0001	0.3	0.0052027		
hsa-miR-302d	346	V\$PAX6_Q2	121	15	0.0025721	2.984	0.3	0.0052027	V\$PAX6_Q1=	

									=>hs a- miR- 302d in clust er clust er20 1_hs a- mir- 302b	
hsa- miR- 183	219	V\$NKX 62_Q2	153	13	0.00258 47	3.2963	0.3	0.00520 27		
hsa- miR- 367	346	V\$MRF 2_01	236	24	0.00260 78	3.1018	0.3	0.00520 27		TFs unmapped
hsa- miR- 133b	333	V\$MY OGNF1 _01	67	10	0.00260 92	3.1261	0.3	0.00520 27		
hsa- miR- 302c	312	V\$PAX 6_Q2	121	14	0.00261 93	2.8657	0.3	0.00520 27	V\$P AX6 _01= =>hs a- miR- 302c in clust er clust er20 1_hs a- mir- 302b	
hsa- miR- 28	124	V\$FRE AC4_01	208	11	0.00263 16	3.9577	0.3	0.00520 27		
hsa- miR- 128a	511	V\$FAC 1_01	207	29	0.00263 66	2.5126	0.3	0.00520 27		
hsa- miR- 320	382	V\$ATF 4_Q2	32	7	0.00264 96	3.8109	0.3	0.00520 27		
hsa- miR- 28	124	V\$HFH 4_01	149	9	0.00266 13	3.2674	0.3	0.00520 27		
hsa- miR- 340	8	V\$E4B P4_01	239	3	0.00266 76	4.9918	0.3	0.00520 27		TFs unmapped
hsa- miR- 139	236	V\$FOX P1_01	195	16	0.00267 74	3.0152	0.3	0.00520 27		TFs unmapped
hsa- miR- 146b	106	V\$PAX 1_B	83	6	0.00268 52	3.9143	0.3	0.00520 27		TFs unmapped

hsa-miR-223	139	V\$OCT 1_01	159	10	0.00269 16	3.0261	0.3	0.00520 27		
hsa-miR-106b	574	V\$TEF _Q6	185	29	0.00269 51	2.6737	0.3	0.00520 27		
hsa-miR-96	544	V\$AHR _01	71	14	0.00273 42	3.0491	0.3	0.00520 27	V\$A HR AR NT_ 02,V \$AH R_0 1== >hsa - miR- 96 in clust er clust er24 2_hs a- mir- 183	
hsa-miR-93	541	V\$SRE BP1_01	119	20	0.00274 13	2.6497	0.3	0.00520 27		
hsa-miR-369-5p	6	V\$SRF _Q6	87	2	0.00276 13	6.4961	0.3	0.00520 27		
hsa-miR-206	400	V\$PAX 2_01	66	11	0.00278 37	3.976	0.3	0.00520 27		
hsa-miR-369-3p	328	V\$SRF _Q4	28	6	0.00278 88	4.0553	0.3	0.00520 27		
hsa-miR-34c	352	V\$HM EF2_Q6	120	15	0.00279 71	3.0554	0.3	0.00520 27		
hsa-miR-368	110	V\$GAT A1_03	138	8	0.00281 47	3.6466	0.3	0.00520 27		
hsa-miR-204	299	V\$STA T5A_02	155	16	0.00281 76	2.8909	0.3	0.00520 27		
hsa-miR-190	91	V\$MEI S1_01	20	3	0.00283 11	5.8799	0.3	0.00520 27		
hsa-miR-301	468	V\$FOX J2_02	300	36	0.00283 5	2.5991	0.3	0.00520 27		
hsa-miR-122a	116	V\$NFY _C	161	9	0.00285 59	4.0008	0.3	0.00520 27		
hsa-	468	V\$WH	49	10	0.00286	2.9702	0.3	0.00520		TFs

miR-301		N_B			2			27		unmapped
hsa-miR-200a	98	V\$STA T5A_01	91	6	0.00287 9	3.7442	0.3	0.00520 27		
hsa-miR-24	291	V\$EVI1 02	65	9	0.00288 39	3.2148	0.3	0.00520 27		TFs unmapped
hsa-miR-1	402	V\$PAX 2_01	66	11	0.00289 41	3.3301	0.3	0.00520 27		
hsa-miR-196b	134	V\$FOX P1_01	195	11	0.00292 81	3.544	0.3	0.00520 27		TFs unmapped
hsa-miR-34b	246	V\$STA T5A_02	155	14	0.00296 53	3.2874	0.3	0.00520 27		
hsa-miR-21	135	V\$CRE BP1_01	166	10	0.00297 59	3.4454	0.3	0.00520 27		
hsa-miR-135a	325	V\$MY OD_Q6 01	38	7	0.00298 17	3.5348	0.3	0.00520 27		
hsa-miR-25	312	V\$AFP 1_Q6	220	21	0.00298 18	3.0378	0.3	0.00520 27		TFs unmapped
hsa-miR-208	59	V\$NKX 62_Q2	153	6	0.00298 93	3.6915	0.3	0.00520 27		
hsa-miR-133b	333	V\$AFP 1_Q6	220	22	0.00299 63	2.6053	0.3	0.00520 27		TFs unmapped
hsa-miR-221	217	V\$SRF _Q6	87	9	0.00299 69	3.3545	0.3	0.00520 27	V\$SRF_01,V\$SRF_Q6==>hsa-miR-221 in cluster cluster280_hsa-mir-222	
hsa-miR-335	136	V\$HSF 1_01	46	5	0.00301 24	3.8011	0.3	0.00520 27		
hsa-miR-28	124	V\$SOX _Q6	152	9	0.00304 52	3.2082	0.3	0.00520 27		
hsa-miR-	284	V\$RRE B1_01	93	11	0.00304 72	2.8875	0.3	0.00520 27		

142-5p										
hsa-miR-338	203	V\$NKKX 25_01	251	17	0.00306 31	3.2368	0.3	0.00520 27		TFs unmapped
hsa-miR-10a	131	V\$TFIII _Q6	144	9	0.00306 6	3.1338	0.3	0.00520 27		
hsa-miR-148b	321	V\$HFFH 1_01	243	23	0.00307 58	2.8506	0.3	0.00520 27		TFs unmapped
hsa-miR-193b	171	V\$E2F_ 03	37	5	0.00307 69	4.1431	0.3	0.00520 27		
hsa-miR-335	136	V\$RSR FC4_Q 2	139	9	0.00311 1	2.9228	0.3	0.00520 27		TFs unmapped
hsa-miR-368	110	V\$CDX _Q5	240	11	0.00311 47	3.6135	0.3	0.00520 27		
hsa-miR-182	501	V\$OCT 1_03	54	11	0.00311 84	2.9757	0.3	0.00520 27		
hsa-miR-155	178	V\$PBX 1_01	87	8	0.00314 08	3.7017	0.3	0.00520 27		TFs unmapped
hsa-miR-330	343	V\$CDP CR1_01	89	12	0.00314 31	3.0721	0.3	0.00520 27	V\$C DPC R3_ 01= =>hs a- miR- 330 in clust er clust er13 4_hs a- mir- 330	
hsa-miR-196b	134	V\$CDP _01	197	11	0.00316 87	2.7599	0.3	0.00520 27		
hsa-miR-196b	134	V\$MZF 1_02	68	6	0.00317 04	3.8797	0.3	0.00520 27		
hsa-miR-135b	329	V\$MY OD_Q6 _01	38	7	0.00319 37	3.6063	0.3	0.00520 27		
hsa-miR-34c	352	V\$TCF 1P_Q6	87	12	0.00320 82	2.8545	0.3	0.00520 27		TFs unmapped
hsa-miR-331	205	V\$TFII A_Q6	45	6	0.00321 11	3.7854	0.3	0.00520 27		
hsa-	346	V\$MSX	136	16	0.00321	3.1054	0.3	0.00520		TFs

miR-367		1_01			13			27		unmapped
hsa-miR-146a	110	V\$PAX 1_B	83	6	0.00323 3	3.7461	0.3	0.00520 27		TFs unmapped
hsa-miR-369-3p	328	V\$PPA RG_03	70	10	0.00325 04	3.2301	0.3	0.00520 27		TFs unmapped
hsa-miR-133a	318	V\$ALX 4_01	148	16	0.00326 32	3.0573	0.3	0.00520 27		
hsa-miR-107	588	V\$FRE AC7_01	175	28	0.00331 23	2.6385	0.3	0.00520 27		
hsa-miR-193a	174	V\$E2F_ 03	37	5	0.00331 71	3.8708	0.3	0.00520 27		
hsa-miR-133a	318	V\$ALP HACP1_01	135	15	0.00333 88	2.9598	0.3	0.00520 27		TFs unmapped
hsa-miR-128a	511	V\$E4B P4_01	239	32	0.00336 39	2.4768	0.3	0.00520 27		TFs unmapped
hsa-miR-371	19	V\$ZF5_ B	102	3	0.00336 52	5.0412	0.3	0.00520 27		TFs unmapped
hsa-miR-28	124	V\$MEF 2_02	126	8	0.00337 07	3.5723	0.3	0.00520 27		
hsa-miR-32	444	V\$RFX _Q6	79	13	0.00338 69	3.3759	0.3	0.00520 27		hsa-miR-32==> TF cluster 251: V\$EFC_Q6, V\$RFX1_01, V\$RFX1_02, V\$RFX_Q6, (NM_002918)
hsa-miR-122a	116	V\$CDP _01	197	10	0.00339 98	3.1049	0.3	0.00520 27		
hsa-miR-33	264	V\$TCF 1P_Q6	87	10	0.00340 71	3.3271	0.3	0.00520 27		TFs unmapped
hsa-miR-219	173	V\$OCT 1_02	248	15	0.00341 47	3.0898	0.3	0.00520 27		
hsa-miR-29a	540	V\$SPZ 1_01	37	9	0.00341 82	3.3465	0.3	0.00520 27		TFs unmapped
hsa-miR-148a	321	V\$ETS 1_B	72	10	0.00343 19	3.1852	0.3	0.00520 27		

hsa-miR-183	219	V\$EVII_05	72	8	0.0034331	3.5909	0.3	0.0052027		TFs unmapped
hsa-miR-129	204	V\$ATF4_Q2	32	5	0.0034355	4.2891	0.3	0.0052027		
hsa-miR-375	160	V\$PIT1_Q6	120	9	0.003444	3.2096	0.3	0.0052027		
hsa-miR-182	501	V\$RORA1_01	26	7	0.0034584	3.946	0.3	0.0052027		TFs unmapped
hsa-miR-210	15	V\$LYF1_01	132	3	0.0034618	5.7986	0.3	0.0052027		TFs unmapped
hsa-miR-16	577	V\$PAX4_04	91	17	0.0034886	3.3896	0.3	0.0052027		TFs unmapped
hsa-miR-340	8	V\$AREB6_03	72	2	0.003492	7.4809	0.3	0.0052027		TFs unmapped
hsa-miR-33	264	V\$MEF2_04	163	15	0.0034962	3.2358	0.3	0.0052027		
hsa-miR-100	29	V\$S8_01	138	4	0.0034976	5.258	0.3	0.0052027		TFs unmapped
hsa-miR-10a	131	V\$HMEF2_Q6	120	8	0.0034995	2.7663	0.3	0.0052027		
hsa-miR-10b	131	V\$FREAC7_01	175	10	0.003503	3.32	0.3	0.0052027		
hsa-miR-10a	131	V\$FREAC7_01	175	10	0.003503	3.6787	0.3	0.0052027		
hsa-miR-29b	542	V\$SPZ1_01	37	9	0.0035048	3.2875	0.3	0.0052027		TFs unmapped
hsa-miR-30d	626	V\$HNF1_Q6_01	173	29	0.0035082	2.6197	0.3	0.0052027		
hsa-miR-134	88	V\$OCT1_07	262	10	0.0035084	3.5116	0.3	0.0052027		
hsa-miR-93	541	V\$SRY_02	81	15	0.0035129	2.5453	0.3	0.0052027		
hsa-miR-190	91	V\$CREB_Q4	102	6	0.0035164	4.3612	0.3	0.0052027		
hsa-miR-324-5p	48	V\$CAR T1_01	335	8	0.0035588	3.8706	0.3	0.0052027		
hsa-miR-34c	352	V\$PAX8_B	77	11	0.0035695	3.0081	0.3	0.0052027		

hsa-miR-218	417	V\$POU3F2_01	201	24	0.0035766	2.3801	0.3	0.0052027	hsa-miR-218==> TF cluster 226: V\$BRN2_01, V\$OCT_Q6, V\$POU3F2_01, V\$POU3F2_02, hsa-miR-218==> TF cluster 227: V\$POU3F2_01, V\$POU3F2_02, (NM_005604)
hsa-miR-152	323	V\$ETS1_B	72	10	0.0035885	3.5951	0.3	0.0052027	
hsa-miR-33	264	V\$CREB_Q4	102	11	0.00359	3.3021	0.3	0.0052027	
hsa-miR-144	428	V\$FAC1_01	207	25	0.0036002	2.391	0.3	0.0052027	
hsa-miR-144	428	V\$NKX62_Q2	153	20	0.0036099	2.7452	0.3	0.0052027	
hsa-miR-208	59	V\$OCT1_01	159	6	0.0036188	4.0788	0.3	0.0052027	
hsa-miR-29b	542	V\$CDPCR1_01	89	16	0.0036293	2.9614	0.3	0.0052027	
hsa-miR-193b	171	V\$E2F_Q4_01	12	3	0.0036723	5.5816	0.3	0.0052027	hsa-miR-193b==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949)
hsa-let-7f	494	V\$ETS1_B	72	13	0.0036943	2.8659	0.3	0.0052027	hsa-let-7f==> TF cluster

										308: V\$ETS1_ B, V\$ETS_Q 4, (NM_005 238)
hsa-miR-146b	106	V\$TAL1BETA ITF2_0 1	118	7	0.00369 71	3.2103	0.3	0.00520 27		
hsa-miR-339	155	V\$MEI S1BHO XA9_0 2	149	10	0.00370 46	2.6974	0.3	0.00520 27		
hsa-miR-30b	624	V\$PBX 1_02	121	22	0.00370 69	2.5021	0.3	0.00520 27		TFs unmapped
hsa-miR-29c	547	V\$SPZ 1_01	37	9	0.00372 9	3.5278	0.3	0.00520 27		TFs unmapped
hsa-miR-368	110	V\$OCT Q6	282	12	0.00373 16	3.0929	0.3	0.00520 27		
hsa-miR-342	143	V\$OLF 1_01	46	5	0.00374 05	3.9323	0.3	0.00520 27		TFs unmapped
hsa-miR-181c	476	V\$CDP 01	197	26	0.00375 41	2.6685	0.3	0.00520 27	V\$C DP_ 01= =>hs a- miR- 181c in clust er clust er13 0_hs a- mir- 181c	
hsa-miR-368	110	V\$ISRE 01	177	9	0.00376 34	3.4075	0.3	0.00520 27		TFs unmapped
hsa-miR-210	15	V\$SRF Q5_02	136	3	0.00376 68	5.4229	0.3	0.00520 27		
hsa-miR-98	491	V\$AP1 Q4	41	9	0.00377 46	2.7863	0.3	0.00520 27		TFs unmapped
hsa-miR-153	359	V\$E2F_ Q4	36	7	0.00377 98	2.7028	0.3	0.00520 27		TFs unmapped
hsa-miR-20a	571	V\$P53_ 01	85	16	0.00378 34	2.7844	0.3	0.00520 27		
hsa-	178	V\$AFP	220	14	0.00380	2.2471	0.3	0.00520		TFs

miR-155		1_Q6			65			27		unmapped
hsa-miR-34a	351	V\$MY OGNF1_01	67	10	0.00381 88	3.0213	0.3	0.00520 27		
hsa-miR-146b	106	V\$ICS BP_Q6	256	11	0.00382 77	2.9516	0.3	0.00520 27		
hsa-miR-30d	626	V\$PBX 1_02	121	22	0.00385 44	2.2395	0.3	0.00520 27		TFs unmapped
hsa-miR-21	135	V\$IRF1_01	49	5	0.00385 49	4.1659	0.3	0.00520 27	V\$IRF_Q6= =>hsa-miR-21 in cluster cluster115_hsa-mir-21	
hsa-miR-193a	174	V\$E2F_Q4_01	12	3	0.00385 75	5.0486	0.3	0.00520 27	hsa-miR-193a==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949)	
hsa-miR-9	614	V\$MAX_01	22	7	0.00386 37	3.1098	0.3	0.00520 27		TFs unmapped
hsa-miR-129	204	V\$RP5_8_01	96	9	0.00386 98	2.8023	0.3	0.00520 27		
hsa-miR-17-5p	565	V\$AHR_01	71	14	0.00387 02	2.7822	0.3	0.00520 27		
hsa-miR-185	267	V\$HNF1_01	179	16	0.00387 87	2.7864	0.3	0.00520 27		
hsa-miR-219	173	V\$PR_Q2	24	4	0.00388 13	3.6116	0.3	0.00520 27	V\$PR_01,V\$PR_	

									Q2= =>hs a- miR- 219 in clust er clust er22 0_hs a- mir- 219- 1	
hsa- miR- 10a	131	V\$FAC 1_01	207	11	0.00388 82	3.3933	0.3	0.00520 27		
hsa- miR- 10b	131	V\$FAC 1_01	207	11	0.00388 82	3.5922	0.3	0.00520 27		
hsa- miR- 185	267	V\$VDR _Q3	48	7	0.00389 31	3.8458	0.3	0.00520 27		
hsa- miR- 324- 3p	130	V\$BAC H1_01	179	10	0.00389 72	3.3721	0.3	0.00520 27		
hsa- miR- 219	173	V\$POU 6F1_01	302	17	0.00391 53	3.1952	0.3	0.00520 27		TFs unmapped
hsa- let- 7f	494	V\$AP1 _Q4	41	9	0.00393 19	3.0079	0.3	0.00520 27		TFs unmapped
hsa- miR- 185	267	V\$FOX M1_01	132	13	0.00394 73	3.1723	0.3	0.00520 27		TFs unmapped
hsa- miR- 342	143	V\$YY1 _Q6	137	9	0.00394 98	2.7592	0.3	0.00520 27		
hsa- miR- 7	252	V\$PAX 4_01	27	5	0.00395 87	3.2854	0.3	0.00520 27		TFs unmapped
hsa- miR- 125b	370	V\$ETS 2_B	64	10	0.00396 29	3.5117	0.3	0.00520 27	V\$E TS2 _B= =>hs a- miR- 125b in clust er clust er48 _hsa -mir- 125b -1	

hsa-miR-99a	30	V\$S8_01	138	4	0.0039676	4.2069	0.3	0.0052027		TFs unmapped
hsa-miR-29c	547	V\$CDP CR1_01	89	16	0.0039746	3.3063	0.3	0.0052027		
hsa-miR-208	59	V\$HNF 6_Q6	403	10	0.0039833	3.29	0.3	0.0052027		
hsa-miR-31	147	V\$CRE BP1CJ UN_01	65	6	0.003997	3.066	0.3	0.0052027		
hsa-miR-219	173	V\$ATF 3_Q6	135	10	0.0040056	2.4698	0.3	0.0052027		
hsa-miR-15a	585	V\$PAX 4_Q4	91	17	0.0040216	3.1927	0.3	0.0052027		TFs unmapped
hsa-miR-367	346	V\$NFK B_Q6	91	12	0.0040631	3.159	0.3	0.0052027		
hsa-miR-372	560	V\$SRE BP1_01	119	20	0.0040815	2.8102	0.3	0.0052027		
hsa-miR-32	444	V\$RSR FC4_Q2	139	19	0.0040853	2.6621	0.3	0.0052027		TFs unmapped
hsa-miR-320	382	V\$CDP_01	197	22	0.0040936	2.6782	0.3	0.0052027		
hsa-miR-133a	318	V\$E47_01	31	6	0.0040998	3.1332	0.3	0.0052027		TFs unmapped
hsa-miR-204	299	V\$YY1_02	161	16	0.0041204	2.8275	0.3	0.0052027		
hsa-miR-23b	395	V\$NRF 2_Q4	156	19	0.0041228	2.5225	0.3	0.0052027		
hsa-miR-135a	325	V\$NFA T_Q4_01	7	3	0.0041484	4.1684	0.3	0.0052027		
hsa-miR-210	15	V\$EVI1_03	141	3	0.0041708	4.8114	0.3	0.0052027		TFs unmapped
hsa-miR-340	8	V\$SRF_C	79	2	0.0041904	7.5586	0.3	0.0052027		
hsa-miR-20b	563	V\$POU 1F1_Q6	177	27	0.0041905	2.4147	0.3	0.0052027		
hsa-miR-30c	624	V\$IK1_01	93	18	0.0042018	2.5019	0.3	0.0052027		TFs unmapped
hsa-miR-30b	624	V\$IK1_01	93	18	0.0042018	2.6031	0.3	0.0052027		TFs unmapped
hsa-miR-	265	V\$NFK APPAB	49	7	0.004203	3.4255	0.3	0.0052027		

22		65_01								
hsa-miR-192	79	V\$AM EF2_Q6	206	8	0.0042114	4.1067	0.3	0.0052027		
hsa-miR-34c	352	V\$AIR E_02	201	21	0.0042205	2.9621	0.3	0.0052027		
hsa-miR-196b	134	V\$GAT A1_04	121	8	0.0042284	2.9392	0.3	0.0052027		
hsa-miR-302d	346	V\$SP3_Q3	80	11	0.0042295	2.9586	0.3	0.0052027		hsa-miR-302d==> TF cluster 282: V\$SP3_Q3, (NM_003111)
hsa-miR-369-3p	328	V\$E2F_Q3_01	7	3	0.0042584	5.9465	0.3	0.0052027		
hsa-miR-34a	351	V\$STA T5B_01	163	18	0.0042639	2.7908	0.3	0.0052027		
hsa-miR-302c	312	V\$DR3_Q4	42	7	0.0042662	3.4767	0.3	0.0052027		
hsa-miR-30a-5p	625	V\$IK1_01	93	18	0.004274	3.0742	0.3	0.0052027		TFs unmapped
hsa-miR-18b	142	V\$CDP_02	280	14	0.0042871	3.0107	0.3	0.0052027		
hsa-miR-129	204	V\$SP3_Q3	80	8	0.0042901	3.1032	0.3	0.0052027		hsa-miR-129==> TF cluster 282: V\$SP3_Q3, (NM_003111)
hsa-miR-135b	329	V\$NFA T_Q4_01	7	3	0.0042954	3.9563	0.3	0.0052027		
hsa-miR-155	178	V\$PR_Q2	24	4	0.0042986	3.729	0.3	0.0052027		
hsa-miR-190	91	V\$BRN 2_01	219	9	0.0043179	3.524	0.3	0.0052027		
hsa-let-7e	501	V\$AP1_Q4	41	9	0.0043192	2.7887	0.3	0.0052027		TFs unmapped
hsa-miR-302a	342	V\$DEC_Q1	59	9	0.0043356	3.2971	0.3	0.0052027		
hsa-	300	V\$PAX	119	13	0.00434	3.0761	0.3	0.00520		

miR-9-star		_Q6			17			27		
hsa-miR-122a	116	V\$GAT A_C	111	7	0.00434 26	3.1225	0.3	0.00520 27		
hsa-miR-133a	318	V\$E47_ 02	14	4	0.00435 67	5.0268	0.3	0.00520 27		TFs unmapped
hsa-miR-125a	375	V\$ETS 2_B	64	10	0.00436 05	2.8521	0.3	0.00520 27		
hsa-miR-128b	507	V\$SMA D4_Q6	48	10	0.00436 34	2.9295	0.3	0.00520 27		
hsa-miR-103	580	V\$IRF1 01	49	11	0.00436 48	3.2255	0.3	0.00520 27		
hsa-miR-326	261	V\$HTF 01	121	12	0.00436 7	2.9879	0.3	0.00520 27		TFs unmapped
hsa-miR-128a	511	V\$HOX A3_01	158	23	0.00437 71	2.405	0.3	0.00520 27		TFs unmapped
hsa-miR-144	428	V\$HNF 3B_01	145	19	0.00438 56	2.5817	0.3	0.00520 27		TFs unmapped
hsa-miR-325	23	V\$GAB P_B	92	3	0.00439 5	3.8874	0.3	0.00520 27		
hsa-miR-302c	312	V\$ATF 4_Q2	32	6	0.00440 36	3.8968	0.3	0.00520 27		
hsa-miR-18b	142	V\$NFK B_Q6	91	7	0.00440 64	3.3867	0.3	0.00520 27		
hsa-miR-302b-star	240	V\$AFP 1_Q6	220	17	0.00442 24	2.601	0.3	0.00520 27		TFs unmapped
hsa-miR-130a	488	V\$FOX J2_01	137	20	0.00443 52	2.4743	0.3	0.00520 27		
hsa-miR-125b	370	V\$CRE BATF_ Q6	65	10	0.00444 4	2.4894	0.3	0.00520 27		
hsa-miR-92	413	V\$FOX P1_01	195	23	0.00445 46	2.4583	0.3	0.00520 27	V\$F OX P1_01 ==> hsa- miR- 92 in clust er clust er29 2_hs a-	TFs unmapped

									mir-106a	
hsa-miR-122a	116	V\$HNF3ALPHA_Q6	84	6	0.0044624	2.7295	0.3	0.0052027		
hsa-miR-142-5p	284	V\$ZIC2_01	71	9	0.0044946	3.1442	0.3	0.0052027		
hsa-miR-20b	563	V\$SPZ1_01	37	9	0.0045244	3.3441	0.3	0.0052027		TFs unmapped
hsa-miR-135b	329	V\$ELF1_Q6	73	10	0.0045275	3.3752	0.3	0.0052027		
hsa-miR-146a	110	V\$TAL1BETAITF2_01	118	7	0.004539	3.9059	0.3	0.0052027		
hsa-miR-192	79	V\$ARN_T_01	27	3	0.0045477	3.5986	0.3	0.0052027		
hsa-miR-192	79	V\$AP2_Q3	27	3	0.0045477	3.7063	0.3	0.0052027		
hsa-miR-129	204	V\$FREAC3_01	238	16	0.0045523	2.6971	0.3	0.0052027		
hsa-miR-203	316	V\$HNF1_C	154	16	0.0045532	2.6854	0.3	0.0052027		
hsa-miR-367	346	V\$EVI1_03	141	16	0.0046041	2.9437	0.3	0.0052027		TFs unmapped
hsa-miR-9-star	300	V\$IK1_01	93	11	0.0046291	3.1625	0.3	0.0052027		TFs unmapped
hsa-miR-17-5p	565	V\$SPZ1_01	37	9	0.0046326	3.205	0.3	0.0052027		TFs unmapped
hsa-miR-143	174	V\$SOX9_B1	137	10	0.0046336	2.8365	0.3	0.0052027		
hsa-miR-367	346	V\$HNF6_Q6	403	35	0.0046342	2.253	0.3	0.0052027		
hsa-miR-128b	507	V\$PAX4_01	27	7	0.0046517	3.0532	0.3	0.0052027		TFs unmapped
hsa-miR-148b	321	V\$SOX_Q6	152	16	0.0046622	2.7661	0.3	0.0052027		hsa-miR-148b==> TF cluster 280: V\$SOX5_01, V\$SOX_Q6,

									(NM_006940)
hsa-miR-23a	391	V\$STAT A_C	171	20	0.00467 12	2.4179	0.3	0.00520 27	
hsa-miR-302d	346	V\$DEC Q1	59	9	0.00468 03	3.5828	0.3	0.00520 27	
hsa-miR-136	128	V\$CRE B_Q4	102	7	0.00468 15	3.5036	0.3	0.00520 27	
hsa-miR-149	208	V\$LUN 1_Q1	97	9	0.00471 21	4.0113	0.3	0.00520 27	TFs unmapped
hsa-miR-182	501	V\$ATF 1_Q6	73	13	0.00471 32	2.6764	0.3	0.00520 27	
hsa-miR-182	501	V\$CO MP1_0 1	73	13	0.00471 32	2.8209	0.3	0.00520 27	TFs unmapped
hsa-miR-96	544	V\$NFK B_Q6	91	16	0.00472 32	2.7597	0.3	0.00520 27	
hsa-miR-302b -star	240	V\$TEF Q6	185	15	0.00472 49	3.1611	0.3	0.00520 27	
hsa-miR-129	204	V\$E4B P4_Q1	239	16	0.00474 09	2.5652	0.3	0.00520 27	TFs unmapped
hsa-miR-7	252	V\$MEF 2_Q1	211	17	0.00474 2	2.8406	0.3	0.00520 27	V\$ MEF 2_Q4 => hsa- miR- 7 in clust er clust er26 7_hs a- mir- 7-1
hsa-miR-199a -star	420	V\$CEB PB_Q2	117	16	0.00475 18	2.5154	0.3	0.00520 27	
hsa-miR-185	267	V\$ALP HACP1 Q1	135	13	0.00478 57	3.0008	0.3	0.00520 27	TFs unmapped
hsa-miR-199a	151	V\$SRF Q6	87	7	0.00481 21	3.1521	0.3	0.00520 27	V\$S RF_ C== >hsa- miR- 199a

									in clust er clust er17 _hsa- mir- 199a -2 V\$S RF_ Q5_ 01= =>hs a- miR- 199a in clust er clust er12 8_hs a- mir- 199a -1	
hsa- miR- 215	75	V\$OCT 1_Q5_0 1	29	3	0.00482 36	3.9539	0.3	0.00520 27		
hsa- miR- 342	143	V\$FOX P1_01	195	11	0.00482 56	3.3085	0.3	0.00520 27		TFs unmapped
hsa- miR- 339	155	V\$ATF _01	107	8	0.00483 23	3.2618	0.3	0.00520 27		TFs unmapped
hsa- miR- 195	585	V\$TCF 11MAF G_01	164	26	0.00483 3	2.6177	0.3	0.00520 27		hsa-miR- 195==> TF cluster 162: V\$MAF_ Q6_01, V\$TCF11 MAFG_0 1, V\$TCF11 _01, (NM_003 204)
hsa- miR- 15a	585	V\$TCF 11MAF G_01	164	26	0.00483 3	2.7684	0.3	0.00520 27		hsa-miR- 15a==> TF cluster 162: V\$MAF_ Q6_01, V\$TCF11 MAFG_0 1, V\$TCF11 _01,

										(NM_003204)
hsa-miR-190	91	V\$FOX O4_02	265	10	0.00485 03	2.9361	0.3	0.00520 27		
hsa-miR-128a	511	V\$PAX 4_01	27	7	0.00485 91	3.0885	0.3	0.00520 27		TFs unmapped
hsa-miR-146b	106	V\$NCX _01	124	7	0.00486 05	2.737	0.3	0.00520 27		TFs unmapped
hsa-miR-182	501	V\$CP2 _02	21	6	0.00488 62	3.6648	0.3	0.00520 27		
hsa-miR-24	291	V\$ELK 1_01	46	7	0.00490 01	3.3607	0.3	0.00520 27		
hsa-miR-199a	151	V\$PAX 2_01	66	6	0.00491 77	3.6369	0.3	0.00520 27	V\$PAX_Q6=>hsa-miR-199a in cluster128_hsa-mir-199a-1	
hsa-miR-192	79	V\$NRF 2_01	55	4	0.00491 84	3.2121	0.3	0.00520 27		TFs unmapped
hsa-miR-368	110	V\$BRN 2_01	219	10	0.00492 35	3.7851	0.3	0.00520 27		
hsa-miR-324-5p	48	V\$E47_ 02_	14	2	0.00493 9	6.6452	0.3	0.00520 27		TFs unmapped
hsa-miR-152	323	V\$SOX _Q6	152	16	0.00494 98	2.9903	0.3	0.00520 27	V\$SOX9_B1=>hsa-miR-152 in cluster110_hsa-mir-152==>hsa-miR-152==>TF cluster280: V\$SOX5_01, V\$SOX_Q6, (NM_006940)	

									152	
hsa-miR-20a	571	V\$SPZ 1_01	37	9	0.00496 95	3.4624	0.3	0.00520 27		TFs unmapped
hsa-miR-31	147	V\$ER_ Q6_02	30	4	0.00497 14	3.5625	0.3	0.00520 27		
hsa-miR-129	204	V\$OCT 1_07	262	17	0.00498 82	2.7065	0.3	0.00520 27	V\$OCT_ C== >hsa- miR-129 in clust er clust er40 _hsa- mir-129- 2	
hsa-miR-331	205	V\$CDP 01	197	14	0.00501 84	2.8622	0.3	0.00520 27		
hsa-miR-216	112	V\$MEI S1BHO XA9_0 2	149	8	0.00502 38	2.5644	0.3	0.00520 27		
hsa-miR-126-star	274	V\$IRF1 01	49	7	0.00504 7	3.308	0.3	0.00520 27		
hsa-miR-331	205	V\$PPA RA_02	65	7	0.00506 69	3.5071	0.3	0.00520 27		
hsa-miR-149	208	V\$ATF 3_Q6	135	11	0.00506 94	3.2397	0.3	0.00520 27		
hsa-miR-181b	477	V\$HLF 01	181	24	0.00509 05	2.2814	0.3	0.00520 27		TFs unmapped
hsa-miR-184	16	V\$MA ZR_01	2	1	0.00510 49	12.129	0.3	0.00520 27		TFs unmapped
hsa-miR-1	402	V\$GAT A1_02	134	17	0.00511 63	2.3725	0.3	0.00520 27		
hsa-miR-129	204	V\$EGR 3_01	35	5	0.00511 77	3.5043	0.3	0.00520 27		
hsa-miR-194	186	V\$FOX P1_01	195	13	0.00513 37	2.4311	0.3	0.00520 27		TFs unmapped
hsa-miR-133b	333	V\$TAL 1BETA E47_01	31	6	0.00514 08	3.3451	0.3	0.00520 27		TFs unmapped

hsa-miR-133b	333	V\$E47_02	14	4	0.0051411	4.6434	0.3	0.0052027		TFs unmapped
hsa-miR-210	15	V\$IPF1_Q4	152	3	0.0051508	4.1393	0.3	0.0052027		
hsa-miR-30d	626	V\$RSR FC4_Q2	139	24	0.0051785	2.1881	0.3	0.0052027		TFs unmapped

Table 7 - miR-TF significantly co-occurring pairs in the PicTar network, 10kb promoters.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value $<6 \times 10^{-3}$ (FDR q-value=0.3) in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfbsConsFactors track.

Table 8

miR	target num	TF	target num	interaction size	hyper-geometric co-occurrence p-value	Z-score	significant FDR level (q-value)	corresponding FDR p-val	network motifs - FFLs	
									TF->miR	miR->TF
hsa-miR-328	189	V\$ARP1_01	43	11	1.16E-07	7.7216	0.1	9.53E-05		
hsa-miR-28	116	V\$AP1_Q2_01	47	9	3.83E-07	6.6543	0.1	9.53E-05	V\$AP1_Q2_01=>hsa-miR-28 in cluster cluster191_hsa-mir-28	
hsa-miR-144	399	V\$FOX P1_01	94	22	4.78E-07	5.8408	0.1	9.53E-05		TFs unmapped
hsa-miR-326	227	V\$NRSF_01	90	16	5.07E-07	6.4139	0.1	9.53E-05		TFs unmapped
hsa-miR-28	116	V\$PR_02	49	9	5.57E-07	7.4739	0.1	9.53E-05		TFs unmapped
hsa-miR-199a-star	393	V\$FOX P1_01	94	21	1.54E-06	5.6249	0.1	9.53E-05		TFs

										unmapped
hsa-miR-302c	287	V\$E2F_Q3_01	6	5	2.03E-06	12.7795	0.1	9.53E-05		
hsa-miR-302b	288	V\$E2F_Q3_01	6	5	2.07E-06	12.4135	0.1	9.53E-05		
hsa-miR-28	116	V\$ARP1_01	43	8	2.21E-06	8.3627	0.1	9.53E-05		
hsa-miR-135a	297	V\$E12_Q6	14	7	2.86E-06	7.5329	0.1	9.53E-05		
hsa-miR-135b	301	V\$E12_Q6	14	7	3.13E-06	6.832	0.1	9.53E-05		
hsa-miR-302a	316	V\$E2F_Q3_01	6	5	3.28E-06	11.8321	0.1	9.53E-05		
hsa-miR-302d	320	V\$E2F_Q3_01	6	5	3.50E-06	13.4845	0.1	9.53E-05		
hsa-miR-132	176	V\$TEL2_Q6	65	11	4.71E-06	7.367	0.1	9.53E-05		
hsa-miR-212	176	V\$TEL2_Q6	65	11	4.71E-06	6.2384	0.1	9.53E-05		
hsa-miR-299-3p	50	V\$IRF7_01	110	8	4.87E-06	7.385	0.1	9.53E-05		
hsa-miR-33	241	V\$S8_01	91	15	6.61E-06	5.8622	0.1	9.53E-05		TFs unmapped
hsa-miR-101	397	V\$FOX_P1_01	94	20	7.13E-06	5.9303	0.1	9.53E-05		TFs unmapped
hsa-miR-28	116	V\$OCT1_06	66	9	7.46E-06	6.9642	0.1	9.53E-05	V\$OCT1_01==>hsa-miR-28 in cluster cluster191_hsa-mir-28	
hsa-miR-190	84	V\$CAR_T1_01	201	13	7.91E-06	6.5339	0.1	9.53E-05		
hsa-miR-206	371	V\$LMO2COM_02	77	17	8.54E-06	5.9868	0.1	9.53E-05		
hsa-miR-1	373	V\$LMO2COM_02	77	17	9.18E-06	4.8772	0.1	9.53E-05		
hsa-miR-206	371	V\$E12_Q6	14	7	1.26E-05	4.4801	0.1	9.53E-05		
hsa-miR-1	373	V\$E12_Q6	14	7	1.31E-05	5.3677	0.1	9.53E-05		
hsa-miR-199b	171	V\$TCF11MAFG_01	103	13	1.33E-05	5.3654	0.1	9.53E-05		hsa-miR-199b==>TF cluster 162: V\$MAF_Q6_01, V\$TCF11MAFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-	297	V\$SPZ1	30	9	1.65E-	5.5073	0.1	9.53E-05		TFs

135a		01			05					unmapped
hsa-miR-324-5p	43	V\$HOX13_01	43	5	1.68E-05	7.6026	0.1	9.53E-05		TFs unmapped
hsa-miR-190	84	V\$GATA1_04	77	8	1.74E-05	8.1673	0.1	9.53E-05		
hsa-miR-28	116	V\$BACH1_01	112	11	1.80E-05	5.0198	0.1	9.53E-05		
hsa-miR-135b	301	V\$SPZ1_01	30	9	1.84E-05	5.0933	0.1	9.53E-05		TFs unmapped
hsa-miR-26b	435	V\$POU3F2_02	224	36	1.99E-05	4.4423	0.1	9.53E-05		
hsa-miR-139	213	V\$POU1F1_Q6	99	14	2.01E-05	4.9297	0.1	9.53E-05		
hsa-miR-23a	355	V\$FOX P1_01	94	18	2.04E-05	3.625	0.1	9.53E-05		TFs unmapped
hsa-miR-185	236	V\$PPARG_01	57	11	2.08E-05	5.4907	0.1	9.53E-05		TFs unmapped
hsa-miR-23b	359	V\$FOX P1_01	94	18	2.38E-05	4.9752	0.1	9.53E-05		TFs unmapped
hsa-miR-129	185	V\$NKX62_Q2	87	12	2.56E-05	5.4485	0.1	9.53E-05		
hsa-miR-144	399	V\$FOX O3_01	94	19	2.81E-05	6.0714	0.1	9.53E-05		
hsa-miR-199a	134	V\$FREAC7_01	103	11	3.17E-05	4.0771	0.1	9.53E-05		
hsa-miR-339	143	V\$CDP_01	134	13	3.40E-05	5.6586	0.1	9.53E-05		
hsa-miR-26a	428	V\$POU3F2_02	224	35	3.40E-05	4.0091	0.1	9.53E-05		
hsa-miR-331	187	V\$VDR_Q3	39	8	3.53E-05	6.4817	0.1	9.53E-05		
hsa-miR-141	300	V\$STAT A_01	67	13	4.56E-05	5.5819	0.1	9.53E-05		
hsa-miR-142-5p	261	V\$SPZ1_01	30	8	5.01E-05	5.1936	0.1	9.53E-05		TFs unmapped
hsa-miR-194	180	V\$PAX8_01	22	6	5.11E-05	6.157	0.1	9.53E-05		
hsa-miR-199a	134	V\$PAX6_Q2	73	9	5.49E-05	4.7014	0.1	9.53E-05	V\$PAX_Q6==>hsa-miR-199a in cluster cluster128_hsa-mir-199a-1	
hsa-miR-142-5p	261	V\$GATA1_05	89	14	5.69E-05	4.4576	0.1	9.53E-05	V\$GATA1_05==>hsa-miR-142-5p in cluster cluster113_hsa-mir-142	
hsa-miR-93	495	V\$PR_02	49	14	5.89E-05	4.305	0.1	9.53E-05	V\$PR_01==>hsa-miR-93 in cluster cluster23	TFs unmapped

									8_hsa-mir-106b	
hsa-miR-199b	171	V\$FRE AC7_01	103	12	6.49E-05	3.7335	0.1	9.53E-05		
hsa-miR-302a	316	V\$PR_0 2	49	11	6.94E-05	4.6616	0.1	9.53E-05		TFs unmapped
hsa-miR-29a	483	V\$E12_ Q6	14	7	7.12E-05	5.2052	0.1	9.53E-05		
hsa-miR-155	161	V\$FOX P1_01	94	11	7.34E-05	4.941	0.1	9.53E-05		TFs unmapped
hsa-miR-29b	486	V\$E12_ Q6	14	7	7.41E-05	4.8862	0.1	9.53E-05		
hsa-miR-9-star	272	V\$IRF7 01	110	16	7.49E-05	5.7468	0.1	9.53E-05		
hsa-miR-29c	490	V\$E12_ Q6	14	7	7.82E-05	4.6176	0.1	9.53E-05		
hsa-miR-10a	123	V\$POU6 F1_01	169	13	7.93E-05	5.2782	0.1	9.53E-05	V\$POU6 F1_01==>hsa-miR-10a in cluster cluster11 1_hsa-mir-10a	TFs unmapped
hsa-miR-194	180	V\$FOX_ Q2	85	11	7.95E-05	4.9154	0.1	9.53E-05		hsa-miR-194==> TF cluster 96: V\$FOXO 1_02, V\$FOX_ Q2, (NM_002015)
hsa-miR-302a	316	V\$ISRE 01	116	18	8.01E-05	4.6912	0.1	9.53E-05		TFs unmapped
hsa-miR-340	8	V\$PAX4 03	10	2	8.10E-05	7.4593	0.1	9.53E-05		TFs unmapped
hsa-miR-302b	288	V\$ISRE 01	116	17	8.32E-05	3.7629	0.1	9.53E-05		TFs unmapped
hsa-miR-302b	288	V\$NFI_ C	139	19	8.45E-05	3.5759	0.1	9.53E-05		hsa-miR-302b==> TF cluster 36: V\$NFI_ C, V\$NFI_ Q6, V\$NFI_ Q6_01, (NM_002505)
hsa-miR-10b	124	V\$POU6 F1_01	169	13	8.63E-05	4.7742	0.1	9.53E-05	V\$POU6 F1_01==>hsa-miR-10b in cluster cluster14 6_hsa-mir-10b	TFs unmapped

hsa-miR-302d	320	V\$PBX1_01	58	12	8.65E-05	5.0889	0.1	9.53E-05		TFs unmapped
hsa-miR-196b	119	V\$PTF1_BETA_Q6	51	7	9.12E-05	5.9308	0.1	9.53E-05		TFs unmapped
hsa-miR-181a	442	V\$CDC5_01	124	23	9.12E-05	3.9158	0.1	9.53E-05		
hsa-miR-181b	442	V\$CDC5_01	124	23	9.12E-05	5.0599	0.1	9.53E-05		
hsa-miR-181c	442	V\$CDC5_01	124	23	9.12E-05	4.3093	0.1	9.53E-05		
hsa-miR-190	84	V\$CDC5_01	124	9	9.14E-05	5.2103	0.1	9.53E-05		
hsa-miR-302d	320	V\$ISRE_01	116	18	9.42E-05	4.8507	0.1	9.53E-05		TFs unmapped
hsa-miR-328	189	V\$BAC_H1_01	112	13	9.43E-05	4.5444	0.1	9.53E-05		
hsa-miR-145	213	V\$SREBP_Q3	50	9	9.53E-05	5.3764	0.1	9.53E-05		
hsa-miR-206	371	V\$IRF_Q6_01	59	13	0.0001013	4.8351	0.2	0.00073		
hsa-miR-1	373	V\$IRF_Q6_01	59	13	0.000107	4.2355	0.2	0.00073		
hsa-miR-219	160	V\$LEF1_Q6	99	11	0.0001118	5.6778	0.2	0.00073		TFs unmapped
hsa-miR-199a-star	393	V\$POU3_F2_01	105	19	0.0001119	3.7334	0.2	0.00073		
hsa-miR-196a	123	V\$PTF1_BETA_Q6	51	7	0.0001124	5.4566	0.2	0.00073		TFs unmapped
hsa-miR-34b	229	V\$PAX8_B	48	9	0.0001194	5.3898	0.2	0.00073		
hsa-miR-340	8	V\$EVI1_03	74	3	0.0001206	7.8507	0.2	0.00073		TFs unmapped
hsa-miR-324-5p	43	V\$CAR_T1_01	201	8	0.0001232	6.0308	0.2	0.00073		
hsa-miR-183	192	V\$NFM_UE1_Q6	84	11	0.0001274	4.3291	0.2	0.00073		TFs unmapped
hsa-miR-10b	124	V\$IRF2_01	108	10	0.0001287	5.689	0.2	0.00073		
hsa-miR-153	314	V\$NRSF_01	90	15	0.0001294	4.6087	0.2	0.00073		TFs unmapped
hsa-miR-369-3p	308	V\$CDC5_01	124	18	0.0001393	4.2854	0.2	0.00073		
hsa-miR-324-5p	43	V\$PAX6_01	107	6	0.0001504	5.868	0.2	0.00073		
hsa-miR-302b	288	V\$PBX1_01	58	11	0.000152	5.1351	0.2	0.00073		TFs unmapped
hsa-miR-199a-star	393	V\$POU1_F1_Q6	99	18	0.0001588	4.005	0.2	0.00073		
hsa-miR-28	116	V\$MAF_Q6	57	7	0.0001596	5.2942	0.2	0.00073		TFs unmapped
hsa-miR-206	371	V\$YY1_Q6	114	19	0.0001622	3.889	0.2	0.00073		
hsa-miR-199a	134	V\$TCF1_1MAFG_01	103	10	0.000165	4.0913	0.2	0.00073		hsa-miR-199a=> TF cluster 162: V\$MAF_Q6_01,

										V\$TCF11 MAFG_0 1, V\$TCF11 _01, (NM_003 204)
hsa-miR-30e-5p	587	V\$CDC 5_01	124	27	0.00016 96	3.6141	0.2	0.00073		
hsa-miR-206	371	V\$ZIC2 01	54	12	0.00017 16	4.4462	0.2	0.00073		
hsa-miR-30a-5p	583	V\$HIF1 Q5	41	13	0.00017 67	3.961	0.2	0.00073		
hsa-miR-28	116	V\$MEF 2_02	77	8	0.00017 79	4.4392	0.2	0.00073		
hsa-miR-30d	584	V\$HIF1 Q5	41	13	0.00017 98	4.1192	0.2	0.00073		
hsa-miR-1	373	V\$ZIC2 01	54	12	0.00018 06	4.1781	0.2	0.00073		
hsa-miR-367	323	V\$FOXJ 2_01	71	13	0.00018 16	4.6751	0.2	0.00073		
hsa-miR-155	161	V\$FOXJ 2_02	179	15	0.00018 47	4.7661	0.2	0.00073		
hsa-miR-9-star	272	V\$PAX_ Q6	73	12	0.00018 53	4.4003	0.2	0.00073		
hsa-miR-125a	342	V\$CRE BATF_ Q6	59	12	0.00019 41	4.2544	0.2	0.00073		
hsa-miR-302c-star	316	V\$NKX 61_01	103	16	0.00019 67	3.481	0.2	0.00073		
hsa-miR-155	161	V\$HOX 13_01	43	7	0.00019 99	5.1948	0.2	0.00073		TFs unmapped
hsa-miR-193b	161	V\$CRE B_01	43	7	0.00019 99	4.797	0.2	0.00073		
hsa-miR-200b	409	V\$OCT1 _01	97	18	0.00020 07	4.424	0.2	0.00073	V\$OCT1 _Q6==> hsa-miR- 200b in cluster cluster1_ hsa-mir- 200b	
hsa-miR-138	347	V\$GAT A3_01	6	4	0.00020 19	5.4053	0.2	0.00073		
hsa-miR-132	176	V\$OCT1 _06	66	9	0.00020 25	4.2869	0.2	0.00073		
hsa-miR-212	176	V\$OCT1 _06	66	9	0.00020 25	4.551	0.2	0.00073		
hsa-miR-200c	410	V\$OCT1 _01	97	18	0.00020 7	4.9211	0.2	0.00073		
hsa-miR-186	386	V\$CRE B_Q4	94	17	0.00020 76	3.8472	0.2	0.00073		
hsa-miR-328	189	V\$PR_0 2	49	8	0.00020 87	4.3569	0.2	0.00073		TFs unmapped
hsa-miR-9	559	V\$NFY_ Q6_01	23	9	0.00021 97	3.5938	0.2	0.00073		
hsa-miR-30b	582	V\$AFP1 _Q6	114	25	0.00022 83	3.353	0.2	0.00073		TFs unmapped
hsa-miR-30c	582	V\$AFP1 _Q6	114	25	0.00022 83	4.0087	0.2	0.00073		TFs unmapped

hsa-miR-34a	324	V\$IPF1_Q4	82	14	0.0002312	4.4791	0.2	0.00073		
hsa-miR-182	452	V\$HNF3ALPHA_Q6	53	13	0.0002323	4.1212	0.2	0.00073		
hsa-miR-193a	165	V\$CREB_01	43	7	0.0002328	4.9506	0.2	0.00073		
hsa-miR-30a-5p	583	V\$AFP1_Q6	114	25	0.0002346	3.6755	0.2	0.00073	V\$AFP1_Q6==> hsa-miR-30a-5p in cluster cluster224_hsa-mir-30a	TFs unmapped
hsa-miR-210	15	V\$HIF1_Q3	47	3	0.0002396	8.2447	0.2	0.00073		
hsa-miR-153	314	V\$CDP_02	138	19	0.0002399	3.4639	0.2	0.00073		
hsa-miR-206	371	V\$IRF2_01	108	18	0.0002404	3.6161	0.2	0.00073		
hsa-miR-30d	584	V\$AFP1_Q6	114	25	0.000241	3.9053	0.2	0.00073		TFs unmapped
hsa-miR-199a-star	393	V\$FOX_Q2	85	16	0.0002417	3.4314	0.2	0.00073	V\$FOXJ2_01,V\$FOX_Q2==> hsa-miR-199a-star in cluster cluster17_hsa-mir-199a-2	
hsa-miR-7	226	V\$NRSF_01	90	12	0.0002489	4.4919	0.2	0.00073		TFs unmapped
hsa-miR-25	289	V\$FOXJ2_01	71	12	0.0002492	5.1708	0.2	0.00073		
hsa-miR-368	105	V\$E2F_Q4	31	5	0.0002503	4.8199	0.2	0.00073		TFs unmapped
hsa-miR-133b	299	V\$AP1_Q4	25	7	0.0002508	4.4242	0.2	0.00073		TFs unmapped
hsa-miR-138	347	V\$MRF2_01	136	20	0.0002549	4.0924	0.2	0.00073		TFs unmapped
hsa-miR-1	373	V\$IRF2_01	108	18	0.0002571	3.5929	0.2	0.00073		
hsa-miR-30e-5p	587	V\$AFP1_Q6	114	25	0.0002611	4.1905	0.2	0.00073		TFs unmapped
hsa-miR-32	413	V\$RFX_Q6	51	12	0.0002642	5.0467	0.2	0.00073		hsa-miR-32==> TF cluster 251: V\$EFC_Q6, V\$RFX1_01, V\$RFX1_02, V\$RFX_Q6,

									(NM_002918)
hsa-miR-200b	409	V\$IRF_Q6_01	59	13	0.0002701	4.5158	0.2	0.00073	
hsa-miR-200b	409	V\$E12_Q6	14	6	0.000275	4.1197	0.2	0.00073	
hsa-miR-184	16	V\$E47_02	9	2	0.000276	21.4254	0.2	0.00073	TFs unmapped
hsa-miR-200c	410	V\$IRF_Q6_01	59	13	0.0002767	4.5853	0.2	0.00073	
hsa-miR-200c	410	V\$E12_Q6	14	6	0.0002787	4.6261	0.2	0.00073	
hsa-miR-191	27	V\$OCT1_B	125	5	0.000287	5.7322	0.2	0.00073	
hsa-miR-23a	355	V\$RFX_Q6	51	11	0.0002876	5.1189	0.2	0.00073	V\$RFX1_02==>hsa-miR-23a in cluster129_hsa-mir-23a
hsa-miR-148a	297	V\$HFH4_01	91	14	0.0002884	4.0721	0.2	0.00073	
hsa-miR-148b	297	V\$HFH4_01	91	14	0.0002884	3.934	0.2	0.00073	
hsa-miR-369-3p	308	V\$STAT5A_02	88	14	0.0002932	4.0212	0.2	0.00073	
hsa-miR-155	161	V\$FREAC2_01	147	13	0.000297	3.7817	0.2	0.00073	
hsa-miR-155	161	V\$IRF7_01	110	11	0.000304	3.762	0.2	0.00073	
hsa-miR-320	349	V\$FOXO4_02	158	22	0.000306	3.6131	0.2	0.00073	
hsa-miR-142-5p	261	V\$E12_Q6	14	5	0.0003089	3.8589	0.2	0.00073	
hsa-miR-152	299	V\$HFH4_01	91	14	0.0003091	3.6692	0.2	0.00073	
hsa-miR-183	192	V\$E2F_Q3	51	8	0.0003096	4.1133	0.2	0.00073	TFs unmapped
hsa-miR-23b	359	V\$RFX_Q6	51	11	0.000317	4.1526	0.2	0.00073	
hsa-miR-368	105	V\$COMPI_01	50	6	0.0003174	4.919	0.2	0.00073	TFs unmapped
hsa-miR-28	116	V\$FREAC4_01	129	10	0.000322	4.2595	0.2	0.00073	
hsa-miR-190	84	V\$FOXJ2_02	179	10	0.000324	4.3728	0.2	0.00073	
hsa-miR-302c-star	316	V\$OCT1_01	97	15	0.0003268	3.7929	0.2	0.00073	V\$OCT1_06==>hsa-miR-302c-star in cluster201_hsa-mir-302b
hsa-miR-139	213	V\$FOXJ2_01	71	10	0.0003269	4.7252	0.2	0.00073	
hsa-miR-30b	582	V\$IRF7_01	110	24	0.000329	3.2848	0.2	0.00073	

hsa-miR-30c	582	V\$IRF7_01	110	24	0.000329	3.6505	0.2	0.00073		
hsa-miR-302d	320	V\$NIFY_C	139	19	0.0003361	3.8755	0.2	0.00073		hsa-miR-302d==> TF cluster 36: V\$NIFY_C, V\$NIFY_Q6, V\$NIFY_Q6_01, (NM_002505)
hsa-miR-140	169	V\$E2F1 DP2_01	12	4	0.0003362	4.8678	0.2	0.00073		TFs unmapped
hsa-miR-372	511	V\$PR_02	49	13	0.0003372	3.6024	0.2	0.00073		TFs unmapped
hsa-miR-30a-5p	583	V\$IRF7_01	110	24	0.0003376	4.0854	0.2	0.00073		
hsa-miR-34c	323	V\$PAX8_B	48	10	0.0003423	4.1813	0.2	0.00073		
hsa-miR-302a	316	V\$PBX1_01	58	11	0.0003428	4.6964	0.2	0.00073		TFs unmapped
hsa-miR-30d	584	V\$IRF7_01	110	24	0.0003464	3.469	0.2	0.00073		
hsa-miR-130a	451	V\$PITX2_Q2	100	19	0.0003467	3.7129	0.2	0.00073		
hsa-miR-208	56	V\$CDP_01	134	7	0.0003486	4.7407	0.2	0.00073		
hsa-miR-150	168	V\$CREBATF_Q6	59	8	0.0003491	4.719	0.2	0.00073		
hsa-miR-199b	171	V\$PAX6_Q2	73	9	0.0003548	4.2756	0.2	0.00073		
hsa-miR-200b	409	V\$HFH1_01	146	23	0.0003572	3.844	0.2	0.00073		TFs unmapped
hsa-miR-30b	582	V\$CDC5_01	124	26	0.0003662	3.4859	0.2	0.00073		
hsa-miR-30c	582	V\$CDC5_01	124	26	0.0003662	3.6839	0.2	0.00073		
hsa-miR-144	399	V\$POU6F1_01	169	25	0.000369	3.3222	0.2	0.00073		TFs unmapped
hsa-miR-200c	410	V\$HFH1_01	146	23	0.00037	4.4083	0.2	0.00073		TFs unmapped
hsa-miR-369-3p	308	V\$POU6F1_01	169	21	0.000371	3.3029	0.2	0.00073		TFs unmapped
hsa-miR-218	384	V\$POU1F1_Q6	99	17	0.0003712	3.8702	0.2	0.00073		
hsa-miR-375	153	V\$CDP_02	138	12	0.000373	4.1747	0.2	0.00073		
hsa-miR-30e-5p	587	V\$IRF7_01	110	24	0.000374	3.9012	0.2	0.00073		
hsa-miR-30a-5p	583	V\$CDC5_01	124	26	0.0003763	3.2025	0.2	0.00073		
hsa-miR-302d	320	V\$PR_02	49	10	0.0003789	3.6183	0.2	0.00073		TFs unmapped
hsa-miR-30b	582	V\$IRF_Q6	98	22	0.0003794	3.792	0.2	0.00073		hsa-miR-30b==> TF cluster

									152: V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 460)
hsa-miR- 30c	582	V\$IRF_ Q6	98	22	0.00037 94	3.7815	0.2	0.00073	hsa-miR- 30c==> TF cluster 152: V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 460)
hsa-miR- 149	193	V\$ETS_ Q4	11	4	0.00038 27	5.4898	0.2	0.00073	
hsa-miR- 208	56	V\$TEF_ Q6	97	6	0.00038 65	4.7489	0.2	0.00073	
hsa-miR- 30d	584	V\$CDC 5_01	124	26	0.00038 66	3.4598	0.2	0.00073	
hsa-miR- 30a-5p	583	V\$IRF_ Q6	98	22	0.00038 87	4.092	0.2	0.00073	hsa-miR- 30a- 5p==> TF cluster 152: V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 460)
hsa-miR- 30d	584	V\$IRF_ Q6	98	22	0.00039 81	4.0406	0.2	0.00073	hsa-miR- 30d==> TF cluster 152: V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 460)
hsa-miR- 23a	355	V\$IRF_ Q6	98	16	0.00041 11	3.5496	0.2	0.00073	hsa-miR- 23a==> TF cluster 150: V\$IRF1_ 01, V\$IRF_Q 6, V\$IRF_Q 6_01, hsa- miR- 23a==> TF cluster 151: V\$IRF2_ 01,

									V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 198 NM_0021 99)
hsa-miR- 194	180	V\$MRF 2_01	136	13	0.00041 15	4.1814	0.2	0.00073	TFs unmapped
hsa-miR- 34b	229	V\$AP1_ Q4	25	6	0.00041 75	4.4182	0.2	0.00073	TFs unmapped
hsa-miR- 144	399	V\$TGIF _01	63	13	0.00041 98	4.131	0.2	0.00073	hsa-miR- 144==> TF cluster 291: V\$TGIF_ 01, (NM_003 244)
hsa-miR- 194	180	V\$FOXJ 2_01	71	9	0.00042	4.5835	0.2	0.00073	
hsa-miR- 30c	582	V\$MEF 2_03	50	14	0.00042 31	3.789	0.2	0.00073	V\$HME F2_Q6= =>hsa- miR-30c in cluster cluster5_ hsa-mir- 30e
hsa-miR- 30b	582	V\$MEF 2_03	50	14	0.00042 31	3.8678	0.2	0.00073	
hsa-miR- 30e-5p	587	V\$IRF_ Q6	98	22	0.00042 79	3.5867	0.2	0.00073	hsa-miR- 30e- 5p==> TF cluster 152: V\$IRF_Q 6, V\$IRF_Q 6_01, (NM_002 460)
hsa-miR- 30a-5p	583	V\$MEF 2_03	50	14	0.00043 07	3.5846	0.2	0.00073	
hsa-miR- 30d	584	V\$MEF 2_03	50	14	0.00043 84	3.9404	0.2	0.00073	
hsa-miR- 323	217	V\$YY1_ Q6	114	13	0.00044 57	3.914	0.2	0.00073	
hsa-miR- 139	213	V\$AHR ARNT_0 1	74	10	0.00046	3.4378	0.2	0.00073	
hsa-miR- 30e-5p	587	V\$MEF 2_03	50	14	0.00046 21	3.4833	0.2	0.00073	V\$HMEF2_Q6==> hsa-miR-30e-5p in cluster cluster5_hsa-mir- 30e
hsa-miR- 183	192	V\$SOX5 _01	54	8	0.00046 3	3.6501	0.2	0.00073	V\$SOX_Q6==>hsa -miR-183 in cluster

									cluster242_hsa-mir-183
hsa-miR-23b	359	V\$IRF_Q6	98	16	0.0004659	3.9619	0.2	0.00073	hsa-miR-23b==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-23b==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_01, (NM_002198 NM_002199)
hsa-miR-30a-3p	204	V\$OCT_Q6	205	18	0.0004669	3.5097	0.2	0.00073	V\$POU3F2_01==>hsa-miR-30a-3p in cluster224_hsa-mir-30a
hsa-miR-30e-3p	204	V\$OCT_Q6	205	18	0.0004669	3.5721	0.2	0.00073	hsa-miR-30e-3p==> TF cluster 215: V\$OCT_Q6, (NM_006237)
hsa-miR-217	159	V\$ELK1_02	36	6	0.0004746	4.9207	0.2	0.00073	
hsa-miR-135a	297	V\$ZIC2_01	54	10	0.0004751	3.7719	0.2	0.00073	
hsa-miR-122a	110	V\$FOX_O3_01	94	8	0.0004913	5.0029	0.2	0.00073	
hsa-miR-204	278	V\$AFP1_Q6	114	15	0.0004918	3.7938	0.2	0.00073	TFs unmapped
hsa-miR-324-3p	116	V\$BAC_H1_01	112	9	0.0004965	4.027	0.2	0.00073	
hsa-miR-331	187	V\$MZF1_02	56	8	0.0004996	4.392	0.2	0.00073	
hsa-miR-25	289	V\$OCT1_02	146	18	0.0005011	3.7002	0.2	0.00073	
hsa-miR-148a	297	V\$FOX_Q2	85	13	0.0005022	3.9418	0.2	0.00073	hsa-miR-148a==>

									TF cluster 83: V\$FOX_ Q2, (NM_004 514)
hsa-miR- 148b	297	V\$FOX_ Q2	85	13	0.00050 22	3.444	0.2	0.00073	hsa-miR- 148b==> TF cluster 83: V\$FOX_ Q2, (NM_004 514)
hsa-miR- 368	105	V\$CDC 5_01	124	9	0.00050 38	4.498	0.2	0.00073	
hsa-miR-1	373	V\$YY1_ Q6	114	18	0.00050 95	3.5733	0.2	0.00073	
hsa-miR- 183	192	V\$AFP1 Q6	114	12	0.00051 05	4.3577	0.2	0.00073	TFs unmapped
hsa-miR- 325	22	V\$HIF1 Q5	41	3	0.00051 93	8.6254	0.2	0.00073	
hsa-miR- 135b	301	V\$ZIC2 01	54	10	0.00052 83	3.8581	0.2	0.00073	
hsa-miR- 152	299	V\$FOX_ Q2	85	13	0.00053 55	3.8475	0.2	0.00073	hsa-miR- 152==> TF cluster 83: V\$FOX_ Q2, (NM_004 514)
hsa-miR- 30e-3p	204	V\$MEF 2_04	93	11	0.00053 6	4.5049	0.2	0.00073	V\$HMEF2_Q6==> hsa-miR-30e-3p in cluster cluster5_hsa- mir-30e
hsa-miR- 30a-3p	204	V\$MEF 2_04	93	11	0.00053 6	4.1096	0.2	0.00073	
hsa-miR- 29a	483	V\$ZIC2 01	54	13	0.00054 23	3.8534	0.2	0.00073	
hsa-miR- 129	185	V\$NKX 61_01	103	11	0.00056 53	3.6022	0.2	0.00073	V\$NKX61_01==>h sa-miR-129 in cluster cluster40_hsa-mir- 129-2
hsa-miR- 30d	584	V\$HNF3 B_01	75	18	0.00056 8	3.9387	0.2	0.00073	TFs unmapped
hsa-miR- 128b	474	V\$POU1 F1_Q6	99	19	0.00056 83	3.7289	0.2	0.00073	
hsa-miR- 29b	486	V\$ZIC2 01	54	13	0.00057 56	3.7939	0.2	0.00073	
hsa-miR- 122a	110	V\$E47_ 02	9	3	0.00057 95	9.2366	0.2	0.00073	TFs unmapped
hsa-miR- 10a	123	V\$IRF2 _01	108	9	0.00058 43	3.781	0.2	0.00073	V\$IRF2_01==>hsa- miR-10a in cluster cluster111_hsa-mir- 10a
hsa-miR- 342	129	V\$NKX 61_01	103	9	0.00058 43	3.8966	0.2	0.00073	
hsa-miR-	123	V\$TFIII	108	9	0.00058	3.1626	0.2	0.00073	

10a		Q6			43					
hsa-miR-301	436	V\$S8_01	91	17	0.0005846	3.6896	0.2	0.00073		TFs unmapped
hsa-miR-214	377	V\$E47_01	23	7	0.0005883	4.0398	0.2	0.00073		TFs unmapped
hsa-miR-32	413	V\$FOXJ2_01	71	14	0.0005912	5.0346	0.2	0.00073		
hsa-let-7g	457	V\$AP1_Q4	25	8	0.0006024	3.8485	0.2	0.00073		TFs unmapped
hsa-miR-326	227	V\$GCNF_01	72	10	0.0006085	4.3447	0.2	0.00073		
hsa-miR-211	284	V\$AFP1_Q6	114	15	0.000616	4.1343	0.2	0.00073		TFs unmapped
hsa-miR-129	185	V\$CDP_02	138	13	0.0006167	3.08	0.2	0.00073	V\$CDP_01==>hsa-miR-129 in cluster cluster40_hsa-mir-129-2	
hsa-miR-324-5p	43	V\$HFH4_01	91	5	0.0006182	4.3528	0.2	0.00073		
hsa-miR-29c	490	V\$ZIC2_01	54	13	0.0006228	4.5839	0.2	0.00073		
hsa-miR-34b	229	V\$E2F1_Q3_01	18	5	0.0006242	4.4512	0.2	0.00073		
hsa-miR-198	228	V\$SRF_01	85	11	0.0006297	3.8009	0.2	0.00073		hsa-miR-198==>TF cluster 267: V\$SRF_01, V\$SRF_C, V\$SRF_Q4, V\$SRF_Q5_01, V\$SRF_Q5_02, V\$SRF_Q6, (NM_003131)
hsa-miR-302b	288	V\$SOX_Q6	101	14	0.00063	3.6326	0.2	0.00073		
hsa-miR-128a	478	V\$POU1F1_Q6	99	19	0.0006308	3.5595	0.2	0.00073		
hsa-miR-193b	161	V\$AP1_Q4	25	5	0.0006339	5.1762	0.2	0.00073		TFs unmapped
hsa-miR-219	160	V\$SRY_02	52	7	0.0006428	3.9955	0.2	0.00073		
hsa-miR-135a	297	V\$MYOD_Q6_01	29	7	0.0006496	4.1199	0.2	0.00073		
hsa-miR-190	84	V\$OCT1_Q3	27	4	0.0006515	6.094	0.2	0.00073		
hsa-miR-144	399	V\$FREAC3_01	156	23	0.0006609	3.4816	0.2	0.00073		
hsa-miR-206	371	V\$CREBP1CJUN_01	62	12	0.000665	3.6142	0.2	0.00073		
hsa-miR-	441	V\$S8_0	91	17	0.00066	3.6553	0.2	0.00073		TFs

130b		1			64					unmapped
hsa-miR-10a	123	V\$IRF7_01	110	9	0.0006685	4.0339	0.2	0.00073	V\$IRF7_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a	
hsa-miR-136	119	V\$EVI1_06	70	7	0.000675	4.5229	0.2	0.00073	V\$EVI1_04==>h	TFs unmapped
hsa-miR-103	542	V\$CDP CR3HD_01	27	9	0.0006954	4.5035	0.2	0.00073		
hsa-miR-1	373	V\$CRE BP1CJUN_01	62	12	0.0006978	3.4124	0.2	0.00073		
hsa-miR-190	84	V\$NKX22_01	72	6	0.0006979	3.7032	0.2	0.00073		
hsa-miR-7	226	V\$ETS_Q4	11	4	0.0006986	5.6187	0.2	0.00073		
hsa-miR-30b	582	V\$HIF1_Q5	41	12	0.0006987	3.7908	0.2	0.00073		
hsa-miR-30c	582	V\$HIF1_Q5	41	12	0.0006987	3.3614	0.2	0.00073		
hsa-miR-32	413	V\$ETS_Q4	11	5	0.0006988	4.5134	0.2	0.00073		hsa-miR-32==> TF cluster 72: V\$ETS_Q4, (NM_002017)
hsa-miR-135b	301	V\$MYOD_Q6_01	29	7	0.0007039	4.4658	0.2	0.00073		
hsa-miR-320	349	V\$HFH1_01	146	20	0.0007077	3.1924	0.2	0.00073		TFs unmapped
hsa-miR-122a	110	V\$CDC5_01	124	9	0.000709	4.5399	0.2	0.00073		
hsa-miR-10b	124	V\$IRF7_01	110	9	0.000709	4.238	0.2	0.00073		
hsa-miR-193a	165	V\$AP1_Q4	25	5	0.0007091	5.2495	0.2	0.00073		TFs unmapped
hsa-let-7i	469	V\$AP1_Q4	25	8	0.0007171	3.4533	0.2	0.00073		TFs unmapped
hsa-miR-124a	524	V\$FOXJ2_01	71	16	0.0007236	3.6289	0.2	0.00073	V\$FOXJ2_02==>hsa-miR-124a in cluster cluster251_hsa-mir-124a-1	
hsa-miR-302c	287	V\$NFY_C	139	17	0.0007255	3.4744	0.2	0.00073		hsa-miR-302c==> TF cluster 36: V\$NFY_C, V\$NFY_Q6,

										V\$NIFY_Q6_01, (NM_002505)
hsa-miR-144	399	V\$CDP_02	138	21	0.0007382	3.5536	0.3	0.00218		
hsa-miR-130b	441	V\$PITX2_Q2	100	18	0.0007416	3.2184	0.3	0.00218		
hsa-miR-367	323	V\$NFKB_Q6	62	11	0.0007501	4.2245	0.3	0.00218		
hsa-miR-199b	171	V\$SREBP_Q3	50	7	0.0007504	3.7224	0.3	0.00218		
hsa-miR-30e-5p	587	V\$HIF1_Q5	41	12	0.0007551	3.4819	0.3	0.00218		
hsa-miR-302c	287	V\$PR_02	49	9	0.0007563	3.7171	0.3	0.00218		TFs unmapped
hsa-miR-183	192	V\$PAX8_01	22	5	0.000758	4.8055	0.3	0.00218		
hsa-miR-29a	483	V\$LMO2COM_02	77	16	0.0007597	3.348	0.3	0.00218		
hsa-miR-107	549	V\$CDPCR3HD_01	27	9	0.0007643	4.2808	0.3	0.00218		
hsa-miR-194	180	V\$TST1_01	93	10	0.0007711	3.686	0.3	0.00218		
hsa-miR-134	79	V\$AML_Q6	30	4	0.0007799	5.9099	0.3	0.00218		
hsa-miR-132	176	V\$CEBP_Q2	49	7	0.0007865	3.9765	0.3	0.00218		
hsa-miR-212	176	V\$CEBP_Q2	49	7	0.0007865	3.6736	0.3	0.00218		
hsa-miR-140	169	V\$AP1_Q4	25	5	0.0007908	5.6034	0.3	0.00218		TFs unmapped
hsa-miR-302a	316	V\$NIFY_C	139	18	0.0007983	3.5476	0.3	0.00218		hsa-miR-302a==> TF cluster 36: V\$NIFY_C, V\$NIFY_Q6, V\$NIFY_Q6_01, (NM_002505)
hsa-miR-136	119	V\$HNF4_01	35	5	0.0007998	4.8718	0.3	0.00218		
hsa-miR-20b	510	V\$MYOD_Q6_01	29	9	0.0008007	4.3468	0.3	0.00218		
hsa-miR-93	495	V\$E2F_Q3_01	6	4	0.0008034	6.5479	0.3	0.00218	V\$E2F_01, V\$E2F_03==> hsa-miR-93 in cluster cluster23 8_hsa-mir-106b	hsa-miR-93==> TF cluster 58: V\$E2F1_Q3_01, V\$E2F1_Q4, V\$E2F1_Q4_01,

									V\$E2F1_Q6, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02, V\$E2F_03, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-93==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949 NM_005225)
hsa-miR-128b	474	V\$E2F_Q4	31	9	0.0008051	3.8938	0.3	0.00218	TFs unmapped
hsa-miR-206	371	V\$ATF_B	119	18	0.0008089	3.6453	0.3	0.00218	TFs unmapped
hsa-let-7f	448	V\$ETS1_B	53	12	0.0008101	3.9529	0.3	0.00218	hsa-let-7f==> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-10a	123	V\$WHN_B	34	5	0.0008107	4.1994	0.3	0.00218	TFs unmapped
hsa-miR-17-5p	511	V\$MYOD_Q6_01	29	9	0.0008122	4.3459	0.3	0.00218	
hsa-miR-29b	486	V\$LMO2COM_02	77	16	0.0008128	3.7078	0.3	0.00218	
hsa-miR-320	349	V\$CHX10_01	116	17	0.0008158	3.6306	0.3	0.00218	
hsa-miR-133a	285	V\$E47_01	23	6	0.0008259	4.6642	0.3	0.00218	TFs unmapped
hsa-miR-	287	V\$ISRE	116	15	0.00082	3.6613	0.3	0.00218	TFs

302c		01			73					unmapped
hsa-miR-10b	124	V\$WHN B	34	5	0.00084 11	4.0041	0.3	0.00218		TFs unmapped
hsa-miR-367	323	V\$COR EBINDI NGFAC TOR_Q6	93	14	0.00084 5	4.2825	0.3	0.00218		TFs unmapped
hsa-miR-302c-star	316	V\$ARN T_02	95	14	0.00084 55	3.4423	0.3	0.00218		
hsa-miR-101	397	V\$FOX_ Q2	85	15	0.00085 51	3.3543	0.3	0.00218	V\$FOXO4_02,V\$F REAC2_01==>hsa- miR-101 in cluster cluster6_hsa-mir- 101-1	
hsa-miR-128a	478	V\$E2F_ Q4	31	9	0.00085 59	4.1758	0.3	0.00218		TFs unmapped
hsa-miR-130a	451	V\$S8_0 1	91	17	0.00085 99	3.4996	0.3	0.00218		TFs unmapped
hsa-miR-1	373	V\$ATF_ B	119	18	0.00086 15	3.4645	0.3	0.00218		TFs unmapped
hsa-miR-328	189	V\$NRF2 Q4	106	11	0.00086 35	3.8465	0.3	0.00218		
hsa-miR-135a	297	V\$NRSF 01	90	13	0.00087 84	3.5957	0.3	0.00218		TFs unmapped
hsa-miR-192	74	V\$MYO GNF1_0 1	33	4	0.00088 17	4.7601	0.3	0.00218		
hsa-miR-134	79	V\$E2F_ Q4	31	4	0.00088 59	5.1375	0.3	0.00218		TFs unmapped
hsa-miR-368	105	V\$CDP_ 01	134	9	0.00088 59	4.2534	0.3	0.00218		
hsa-miR-125b	337	V\$CRE B_01	43	9	0.00088 72	4.1949	0.3	0.00218		
hsa-miR-29c	490	V\$LMO 2COM_ 02	77	16	0.00088 86	4.0298	0.3	0.00218		
hsa-miR-128a	478	V\$FOX O3_01	94	18	0.00089 5	3.8948	0.3	0.00218		
hsa-miR-144	399	V\$FOX_ Q2	85	15	0.00090 07	3.3275	0.3	0.00218		hsa-miR- 144==> TF cluster 96: V\$FOXO 1_02, V\$FOX_ Q2, (NM_002 015)
hsa-miR-28	116	V\$FRE AC2_01	147	10	0.00090 79	4.0985	0.3	0.00218		
hsa-miR-372	511	V\$E2F_ Q3_01	6	4	0.00090 82	6.4735	0.3	0.00218		hsa-miR- 372==> TF cluster 58: V\$E2F1_ Q3_01, V\$E2F1_ Q4, V\$E2F1_ Q4_01,

										V\$E2F1_Q6, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02, V\$E2F_03, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-372==>TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949 NM_005225)
hsa-miR-146b	94	V\$NFA T_Q6	12	3	0.00092 04	5.9781	0.3	0.00218		
hsa-miR-126-star	254	V\$OCT1 02	146	16	0.00092 43	3.3181	0.3	0.00218		
hsa-miR-328	189	V\$AP1_Q2_01	47	7	0.00092 84	4.2477	0.3	0.00218		
hsa-miR-133b	299	V\$NRSF_01	90	13	0.00093 5	3.7529	0.3	0.00218		TFs unmapped
hsa-miR-129	185	V\$EVI1_01	77	9	0.00093 73	4.0754	0.3	0.00218		TFs unmapped
hsa-miR-129	185	V\$FOX M1_01	77	9	0.00093 73	3.422	0.3	0.00218		TFs unmapped
hsa-miR-92	383	V\$FOXJ2_01	71	13	0.00094 36	3.7441	0.3	0.00218	V\$FOXJ2_02==>hsa-miR-92 in cluster cluster292_hsa-mir-106a	
hsa-miR-96	500	V\$ATF1_Q6	62	14	0.00095	3.8101	0.3	0.00218		
hsa-miR-132	176	V\$AP1_Q4	25	5	0.00095 06	4.7516	0.3	0.00218	V\$AP1_01,V\$AP1_Q4==>hsa-miR-132 in cluster cluster101_hsa-	TFs unmapped

									mir-212	
hsa-miR-212	176	V\$AP1_Q4	25	5	0.0009506	4.4638	0.3	0.00218	V\$AP1_01,V\$AP1_Q4=>hsa-miR-212 in cluster cluster101_hsa-mir-212	TFs unmapped
hsa-miR-186	386	V\$E2F_Q4	31	8	0.0009539	4.2547	0.3	0.00218		TFs unmapped
hsa-miR-181a	442	V\$ETS_Q4	11	5	0.0009559	4.3499	0.3	0.00218		hsa-miR-181a=> TF cluster 72: V\$ETS_Q4, hsa-miR-181a=> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-181b	442	V\$ETS_Q4	11	5	0.0009559	4.2851	0.3	0.00218		hsa-miR-181b=> TF cluster 72: V\$ETS_Q4, hsa-miR-181b=> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-181c	442	V\$ETS_Q4	11	5	0.0009559	4.5685	0.3	0.00218		hsa-miR-181c=> TF cluster 72: V\$ETS_Q4, hsa-miR-181c=> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)

hsa-miR-369-3p	308	V\$SRF_Q4	22	6	0.0009616	5.2875	0.3	0.00218		
hsa-miR-339	143	V\$CREBP1CJUN_01	62	7	0.0009655	4.4279	0.3	0.00218		
hsa-miR-34a	324	V\$CREB_Q4	94	14	0.0009708	3.8621	0.3	0.00218		
hsa-miR-148b	297	V\$S8_01	91	13	0.0009767	3.5696	0.3	0.00218		TFs unmapped
hsa-miR-190	84	V\$E2F_03	30	4	0.000983	6.2844	0.3	0.00218		
hsa-miR-125a	342	V\$CREB_01	43	9	0.000986	3.1238	0.3	0.00218		
hsa-miR-135b	301	V\$NRSF_01	90	13	0.0009948	4.0031	0.3	0.00218		TFs unmapped
hsa-miR-135a	297	V\$E2F_Q4	31	7	0.0009982	4.1825	0.3	0.00218		TFs unmapped
hsa-miR-22	239	V\$MMEF2_Q6	99	12	0.0009983	3.2784	0.3	0.00218	V\$AMEF2_Q6==> hsa-miR-22 in cluster100_hsa-mir-22	
hsa-miR-219	160	V\$TFIII_Q6	108	10	0.0010017	3.1681	0.3	0.00218		
hsa-miR-103	542	V\$E47_01	23	8	0.0010056	3.6601	0.3	0.00218		TFs unmapped
hsa-miR-302d	320	V\$CREB_Q2	85	13	0.0010145	3.4008	0.3	0.00218		
hsa-let-7f	448	V\$GATA2_01	11	5	0.001017	3.6655	0.3	0.00218		TFs unmapped
hsa-miR-98	448	V\$GATA2_01	11	5	0.001017	5.175	0.3	0.00218		TFs unmapped
hsa-miR-93	495	V\$PPARA_02	43	11	0.0010236	3.8943	0.3	0.00218	V\$DR4_Q2,V\$PPARA_02==>hsa-miR-93 in cluster23_hsa-mir-106b (NM_005036)	
hsa-miR-138	347	V\$TAL1BETAE47_01	20	6	0.0010342	4.3119	0.3	0.00218		TFs unmapped
hsa-miR-330	316	V\$TFIII_Q6	108	15	0.0010475	3.3303	0.3	0.00218		
hsa-miR-338	181	V\$COMPI_01	50	7	0.0010506	4.0558	0.3	0.00218		TFs unmapped
hsa-miR-194	180	V\$POU6F1_01	169	14	0.0010547	3.1167	0.3	0.00218		TFs unmapped
hsa-miR-129	185	V\$CEBPB_01	36	6	0.0010569	3.9752	0.3	0.00218		
hsa-miR-194	180	V\$YY1_Q6	114	11	0.0010609	3.7328	0.3	0.00218		
hsa-miR-133b	299	V\$E47_01	23	6	0.001063	4.3758	0.3	0.00218		TFs unmapped

hsa-miR-21	127	V\$CRE BP1_01	137	10	0.00106 38	3.914	0.3	0.00218		
hsa-miR-182	452	V\$HIF1 Q3	47	11	0.00106 68	3.2658	0.3	0.00218		
hsa-miR-146a	99	V\$NFA T_Q6	12	3	0.00107 05	4.8663	0.3	0.00218		
hsa-miR-372	511	V\$HNF3 _Q6_01	42	11	0.00107 88	3.9392	0.3	0.00218		hsa-miR-372==> TF cluster 127: V\$HNF3 ALPHA_ Q6, V\$HNF3 _Q6, V\$HNF3 _Q6_01, (NM_004 496)
hsa-miR-135b	301	V\$E2F_ Q4	31	7	0.00108 03	4.5629	0.3	0.00218		TFs unmapped
hsa-miR-185	236	V\$VDR Q3	39	7	0.00108 7	3.7861	0.3	0.00218		
hsa-miR-137	326	V\$EV11 _03	74	12	0.00109 21	3.8926	0.3	0.00218	V\$EV11 _04==>h sa-miR- 137 in cluster cluster8_ hsa-mir- 137	TFs unmapped
hsa-miR-142-3p	142	V\$YY1_ 02	123	10	0.00109 5	3.7937	0.3	0.00218	V\$YY1_02==>hsa- miR-142-3p in cluster cluster113_hsa-mir- 142	
hsa-miR-107	549	V\$E47_ 01	23	8	0.00109 51	3.9552	0.3	0.00218		TFs unmapped
hsa-miR-137	326	V\$CIZ_ 01	37	8	0.00110 2	3.9247	0.3	0.00218	V\$CIZ_ 01==>hs a-miR- 137 in cluster cluster8_ hsa-mir- 137	TFs unmapped
hsa-miR-34b	229	V\$EV11 _01	77	10	0.00111 38	4.4956	0.3	0.00218	V\$EV11 _03==>h sa-miR- 34b in cluster cluster47_ hsa- mir-34b	TFs unmapped
hsa-let-7e	457	V\$GAT A2_01	11	5	0.00111 43	3.8766	0.3	0.00218		TFs unmapped
hsa-let-7g	457	V\$GAT A2_01	11	5	0.00111 43	4.6427	0.3	0.00218		TFs unmapped
hsa-miR-34c	323	V\$CEBP C	75	12	0.00113 8	3.8527	0.3	0.00218		

hsa-miR-196b	119	V\$MZF1_02	56	6	0.0011452	4.2326	0.3	0.00218		
hsa-miR-93	495	V\$TFIII_Q6	108	20	0.0011459	3.2084	0.3	0.00218		
hsa-miR-129	185	V\$SP3_Q3	64	8	0.0011545	3.4709	0.3	0.00218		hsa-miR-129==> TF cluster 282: V\$SP3_Q3, (NM_003111)
hsa-let-7c	461	V\$GATA2_01	11	5	0.0011597	4.5895	0.3	0.00218		TFs unmapped
hsa-miR-369-5p	6	V\$SRF_Q6	50	2	0.0011606	7.559	0.3	0.00218		
hsa-miR-199a	134	V\$SREBP_Q3	50	6	0.0011618	3.9354	0.3	0.00218		
hsa-miR-34b	229	V\$HNF4A_01	91	11	0.0011662	4.1682	0.3	0.00218		
hsa-miR-215	71	V\$CREB_Q4	94	6	0.0011734	5.7801	0.3	0.00218		
hsa-miR-145	213	V\$AIRE_02	113	12	0.0011846	3.0669	0.3	0.00218		
hsa-miR-129	185	V\$COMPI_01	50	7	0.0011943	4.3617	0.3	0.00218		TFs unmapped
hsa-miR-148b	297	V\$FOXJ2_01	71	11	0.001207	3.58	0.3	0.00218		
hsa-miR-9-star	272	V\$AFP1_Q6	114	14	0.0012161	3.4859	0.3	0.00218		TFs unmapped
hsa-miR-342	129	V\$AFP1_Q6	114	9	0.001218	4.07	0.3	0.00218		TFs unmapped
hsa-miR-96	500	V\$CREB_Q2	85	17	0.0012262	3.0733	0.3	0.00218	V\$CREB_Q2_01==>hsa-miR-96 in cluster 24_hsa-mir-183	hsa-miR-96==> TF cluster 46: V\$CREB_Q2_01, V\$CREB_Q2_02, V\$CREB_Q2_01, V\$CREB_Q4, V\$CREB_Q4_01, V\$TAXCREB_01, V\$TAXCREB_02, (NM_004379)
hsa-miR-222	190	V\$IRF7_01	110	11	0.0012286	3.6879	0.3	0.00218		
hsa-miR-194	180	V\$OLF1_01	38	6	0.0012303	3.9833	0.3	0.00218		TFs unmapped
hsa-miR-	451	V\$MRF	136	22	0.00123	3.4321	0.3	0.00218		TFs

130a		2_01			48					unmapped
hsa-miR-23b	359	V\$NKX 25_02	181	23	0.00124 35	2.7336	0.3	0.00218		TFs unmapped
hsa-miR-299-3p	50	V\$MEIS 1AHOX A9_01	91	5	0.00124 36	6.0519	0.3	0.00218		
hsa-miR-200b	409	V\$LMO 2COM_ 02	77	14	0.00124 58	3.6695	0.3	0.00218		
hsa-miR-27a	542	V\$AFP1 Q6	114	22	0.00125 08	3.3706	0.3	0.00218		TFs unmapped
hsa-miR-152	299	V\$FOXJ 2_01	71	11	0.00127 49	4.3305	0.3	0.00218		
hsa-miR-200c	410	V\$LMO 2COM_ 02	77	14	0.00127 56	3.7126	0.3	0.00218		
hsa-miR-199a-star	393	V\$OCT_ C	207	27	0.00127 64	2.9866	0.3	0.00218		
hsa-miR-144	399	V\$NRF2 _Q4	106	17	0.00128 67	3.521	0.3	0.00218		hsa-miR-144==> TF cluster 214: V\$MAF_ Q6_01, V\$NRF2_ Q4, (NM_006164)
hsa-miR-184	16	V\$ARE B6_01	19	2	0.00128 91	7.8508	0.3	0.00218		TFs unmapped
hsa-let-7b	472	V\$GAT A2_01	11	5	0.00129 18	3.9965	0.3	0.00218		TFs unmapped
hsa-miR-144	399	V\$HNF3 Q6	54	11	0.00129 18	3.6399	0.3	0.00218		
hsa-miR-328	189	V\$AR_0 2	25	5	0.00131 02	4.0229	0.3	0.00218		
hsa-miR-193a	165	V\$PAX6 _Q2	73	8	0.00131 68	4.2025	0.3	0.00218		
hsa-miR-34a	324	V\$TCF1 P_Q6	66	11	0.00132 02	3.4644	0.3	0.00218		TFs unmapped
hsa-miR-188	105	V\$CAR T1_01	201	11	0.00132 29	4.0065	0.3	0.00218		
hsa-miR-219	160	V\$ATF3 Q6	112	10	0.00132 67	3.1682	0.3	0.00218		
hsa-miR-20a	524	V\$HNF3 _Q6_01	42	11	0.00132 83	4.2987	0.3	0.00218		hsa-miR-20a==> TF cluster 127: V\$HNF3 ALPHA_ Q6, V\$HNF3_ Q6, V\$HNF3_ Q6_01, (NM_004496)
hsa-miR-33	241	V\$EGR2 01	20	5	0.00132 89	4.0545	0.3	0.00218		
hsa-miR-	413	V\$FOX	94	16	0.00133	3.5234	0.3	0.00218		TFs

32		P1_01			26					unmapped
hsa-miR-142-3p	142	V\$POU3 F2_01	105	9	0.00133 86	3.545	0.3	0.00218		
hsa-miR-129	185	V\$RFX_ Q6	51	7	0.00134 61	4.3659	0.3	0.00218		
hsa-miR-320	349	V\$ATF4 Q2	28	7	0.00135 07	4.1324	0.3	0.00218		
hsa-miR-217	159	V\$CRE B_Q4	94	9	0.00135 09	3.2611	0.3	0.00218		
hsa-miR-10a	123	V\$OLF1 01	38	5	0.00136 28	5.3032	0.3	0.00218		TFs unmapped
hsa-miR-25	289	V\$PAX3 01	74	11	0.00137 05	3.9507	0.3	0.00218		
hsa-miR-21	127	V\$HNF4 01_B	37	5	0.00139 02	5.639	0.3	0.00218		
hsa-miR-106b	527	V\$HNF3 _Q6_01	42	11	0.00139 23	4.2389	0.3	0.00218		hsa-miR-106b==> TF cluster 127: V\$HNF3 ALPHA_ Q6, V\$HNF3 _Q6, V\$HNF3 _Q6_01, (NM_004 496)
hsa-miR-206	371	V\$HNF1 C	95	15	0.00139 41	3.3298	0.3	0.00218		
hsa-miR-141	300	V\$OCT1 07	166	19	0.00139 74	2.9315	0.3	0.00218		
hsa-miR-10b	124	V\$OLF1 01	38	5	0.00141 3	5.4208	0.3	0.00218		TFs unmapped
hsa-miR-331	187	V\$PPAR A_01	51	7	0.00143 29	4.0407	0.3	0.00218		
hsa-miR-129	185	V\$EGR3 01	26	5	0.00143 45	3.8617	0.3	0.00218		
hsa-miR-299-3p	50	V\$CRE B_Q4	94	5	0.00143 85	4.902	0.3	0.00218		
hsa-miR-9-star	272	V\$CHX 10_01	116	14	0.00144 25	3.6119	0.3	0.00218		
hsa-miR-194	180	V\$HNF3 ALPHA_ _Q6	53	7	0.00144 63	3.4269	0.3	0.00218		hsa-miR-194==> TF cluster 127: V\$HNF3 ALPHA_ Q6, V\$HNF3 _Q6, V\$HNF3 _Q6_01, (NM_004 496)
hsa-miR-302c	287	V\$SP3_ Q3	64	10	0.00144 83	3.2214	0.3	0.00218		hsa-miR-302c==> TF cluster 282: V\$SP3_Q

									3, (NM_003111)
hsa-miR-196a	123	V\$MMEF2_Q6	99	8	0.0014483	3.7379	0.3	0.00218	V\$MEF2_Q3==>hsa-miR-196a in cluster cluster53_hsa-mir-196a-2
hsa-miR-215	71	V\$IRF_Q6	98	6	0.0014575	3.8395	0.3	0.00218	
hsa-miR-34b	229	V\$SOX5_01	54	8	0.0014735	3.98	0.3	0.00218	
hsa-miR-155	161	V\$EV11_04	94	9	0.0014748	3.6163	0.3	0.00218	TFs unmapped
hsa-miR-323	217	V\$PPARG_01	57	8	0.0014947	3.9238	0.3	0.00218	TFs unmapped
hsa-miR-190	84	V\$OCT1_02	146	8	0.0015014	3.7273	0.3	0.00218	
hsa-miR-194	180	V\$FREAC3_01	156	13	0.0015055	3.1378	0.3	0.00218	
hsa-miR-22	239	V\$CMYB_01	52	8	0.0015069	3.3864	0.3	0.00218	V\$MYB_Q3==>hsa-miR-22 in cluster cluster100_hsa-mir-22
hsa-miR-193b	161	V\$E2F_03	30	5	0.0015127	5.8862	0.3	0.00218	
hsa-miR-30b	582	V\$HNF3B_01	75	17	0.0015283	3.3339	0.3	0.00218	TFs unmapped
hsa-miR-30c	582	V\$HNF3B_01	75	17	0.0015283	3.2233	0.3	0.00218	TFs unmapped
hsa-miR-206	371	V\$OCT1_03	27	7	0.0015326	4.0468	0.3	0.00218	
hsa-miR-339	143	V\$STAT_A_01	67	7	0.0015344	4.5006	0.3	0.00218	
hsa-miR-206	371	V\$EV11_01	77	13	0.0015364	4.0687	0.3	0.00218	TFs unmapped
hsa-miR-133b	299	V\$MYOGNF1_01	33	7	0.0015382	3.9028	0.3	0.00218	
hsa-miR-101	397	V\$POU1F1_Q6	99	16	0.0015479	3.366	0.3	0.00218	
hsa-miR-30a-5p	583	V\$HNF3B_01	75	17	0.0015575	3.3262	0.3	0.00218	V\$HNF3B_01,V\$HNF3_Q6==>hsa-miR-30a-5p in cluster cluster224_hsa-mir-30a
hsa-miR-302a	316	V\$SOX_Q6	101	14	0.0015584	3.5478	0.3	0.00218	
hsa-miR-193a	165	V\$CEBP_C	75	8	0.0015719	4.0061	0.3	0.00218	
hsa-miR-218	384	V\$PR_01	49	10	0.0015722	3.5091	0.3	0.00218	V\$PR_Q2==>hsa-miR-218 in cluster

									cluster21 6_hsa- mir-218- 2	
hsa-miR-1	373	V\$OCT1_03	27	7	0.0015814	4.5194	0.3	0.00218	V\$OCT1_B==>hsa-miR-1 in cluster cluster122_hsa-mir-1-2	
hsa-miR-302c	287	V\$DEC_Q1	44	8	0.0015873	3.6369	0.3	0.00218		
hsa-miR-331	187	V\$LYF1_01	82	9	0.0015913	4.2102	0.3	0.00218		TFs unmapped
hsa-miR-323	217	V\$FOXJ2_01	71	9	0.0016058	3.4903	0.3	0.00218		
hsa-miR-199a-star	393	V\$FOXJ2_02	179	24	0.0016087	2.6908	0.3	0.00218	V\$FOXJ2_01,V\$FOX_Q2==>hsa-miR-199a-star in cluster cluster17_hsa-mir-199a-2	
hsa-miR-200c	410	V\$SOX5_01	54	11	0.0016118	3.3372	0.3	0.00218		
hsa-miR-1	373	V\$EVI1_01	77	13	0.0016132	3.9081	0.3	0.00218	V\$EVI1_03,V\$EVI1_04==>hsa-miR-1 in cluster cluster122_hsa-mir-1-2	TFs unmapped
hsa-miR-28	116	V\$AR_02	25	4	0.0016184	3.9357	0.3	0.00218		
hsa-miR-194	180	V\$SEF1_C	40	6	0.0016213	3.962	0.3	0.00218		TFs unmapped
hsa-miR-122a	110	V\$DEC_Q1	44	5	0.0016215	4.3785	0.3	0.00218		hsa-miR-122a==>TF cluster 23: V\$DEC_Q1, (NM_030762)
hsa-miR-302b	288	V\$DEC_Q1	44	8	0.0016231	4.3094	0.3	0.00218		
hsa-miR-328	189	V\$OCT1_06	66	8	0.0016236	3.8581	0.3	0.00218		
hsa-miR-320	349	V\$CDP_01	134	18	0.0016265	3.0814	0.3	0.00218		
hsa-miR-144	399	V\$POU1_F1_Q6	99	16	0.0016313	3.6659	0.3	0.00218		
hsa-miR-199b	171	V\$HFH1_01	146	12	0.0016582	3.2998	0.3	0.00218		TFs unmapped
hsa-miR-340	8	V\$DEC_Q1	44	2	0.0016611	10.3028	0.3	0.00218		
hsa-miR-190	84	V\$FOX_Q2	85	6	0.0016716	3.9172	0.3	0.00218		
hsa-miR-323	217	V\$PBX1_01	58	8	0.0016769	3.7035	0.3	0.00218		TFs unmapped
hsa-miR-	587	V\$HNF3	75	17	0.00167	3.0116	0.3	0.00218		TFs

30e-5p		B_01			9					unmapped
hsa-miR-96	500	V\$ETS_Q4	11	5	0.0016796	4.2128	0.3	0.00218		
hsa-miR-193a	165	V\$E2F_03	30	5	0.0016871	4.7742	0.3	0.00218		
hsa-miR-28	116	V\$NFA_T_Q6	12	3	0.0016942	4.581	0.3	0.00218		
hsa-miR-28	116	V\$NFKB_Q6	62	6	0.0017145	4.5183	0.3	0.00218		
hsa-miR-339	143	V\$TFIII_Q6	108	9	0.0017151	2.8606	0.3	0.00218		
hsa-miR-206	371	V\$GATA1_03	97	15	0.0017295	3.2683	0.3	0.00218		
hsa-miR-299-3p	50	V\$IRF_Q6	98	5	0.0017325	4.6907	0.3	0.00218		
hsa-miR-153	314	V\$HIF1_Q5	41	8	0.0017509	2.9945	0.3	0.00218		
hsa-miR-301	436	V\$PITX2_Q2	100	17	0.0017533	3.2751	0.3	0.00218		
hsa-miR-193b	161	V\$E2F_Q4	31	5	0.001762	4.1417	0.3	0.00218		TFs unmapped
hsa-miR-24	267	V\$OCT_Q6	205	20	0.001815	2.9264	0.3	0.00218		
hsa-miR-199a-star	393	V\$GCM_Q2	41	9	0.0018386	4.0194	0.3	0.00218		TFs unmapped
hsa-miR-148a	297	V\$HFH1_01	146	17	0.0018407	3.4965	0.3	0.00218		TFs unmapped
hsa-miR-148b	297	V\$HFH1_01	146	17	0.0018407	3.2828	0.3	0.00218		TFs unmapped
hsa-miR-92	383	V\$FOXO4_01	27	7	0.0018446	4.4461	0.3	0.00218		
hsa-miR-320	349	V\$POU6F1_01	169	21	0.0018747	2.8736	0.3	0.00218		TFs unmapped
hsa-miR-301	436	V\$MRF2_01	136	21	0.0018866	3.4699	0.3	0.00218		TFs unmapped
hsa-miR-302c	287	V\$SOX_Q6	101	13	0.0018991	3.0644	0.3	0.00218		
hsa-miR-142-5p	261	V\$SRF_01	85	11	0.0019058	3.0794	0.3	0.00218	V\$SRF_Q6==>hsa-miR-142-5p==> TF cluster 267: V\$SRF_01, V\$SRF_C, V\$SRF_Q4, V\$SRF_Q5_01, V\$SRF_Q5_02, V\$SRF_Q6, (NM_003131)	hsa-miR-142-5p==> TF cluster 267: V\$SRF_01, V\$SRF_C
hsa-miR-223	129	V\$PBX1_02	77	7	0.001913	3.6669	0.3	0.00218		TFs unmapped
hsa-miR-142-5p	261	V\$MYOD_Q6_0	29	6	0.0019199	3.529	0.3	0.00218		

		1								
hsa-miR-133a	285	V\$NRSF_01	90	12	0.001959	3.3451	0.3	0.00218		TFs unmapped
hsa-miR-193a	165	V\$E2F_Q4	31	5	0.001964	4.9259	0.3	0.00218		TFs unmapped
hsa-miR-10b	124	V\$NKX61_01	103	8	0.0019676	3.1539	0.3	0.00218		
hsa-miR-320	349	V\$ATF_01	94	14	0.001981	3.0531	0.3	0.00218		TFs unmapped
hsa-miR-148a	297	V\$FREAC2_01	147	17	0.0019829	2.803	0.3	0.00218		
hsa-miR-148b	297	V\$FREAC2_01	147	17	0.0019829	2.8401	0.3	0.00218		
hsa-miR-208	56	V\$SOX5_01	54	4	0.0020048	4.6282	0.3	0.00218		
hsa-miR-141	300	V\$POU3F2_02	224	23	0.0020051	2.8739	0.3	0.00218		
hsa-miR-335	123	V\$AR_03	12	3	0.0020056	5.9024	0.3	0.00218		
hsa-miR-324-5p	43	V\$E47_02	9	2	0.0020301	8.7084	0.3	0.00218		TFs unmapped
hsa-miR-129	185	V\$ATF4_Q2	28	5	0.0020308	4.5941	0.3	0.00218		
hsa-miR-134	79	V\$CDX2_Q5	163	8	0.0020361	4.0413	0.3	0.00218		TFs unmapped
hsa-miR-26b	435	V\$MEIS1BHOXA9_02	93	16	0.0020398	3.5246	0.3	0.00218		
hsa-miR-200b	409	V\$HNF6_Q6	226	29	0.0020516	2.5316	0.3	0.00218		
hsa-miR-142-3p	142	V\$FOXJ2_01	71	7	0.0020698	4.3003	0.3	0.00218		
hsa-miR-129	185	V\$NKX3A_01	70	8	0.0020782	3.4013	0.3	0.00218		
hsa-miR-34c	323	V\$HFH4_01	91	13	0.0020955	3.6977	0.3	0.00218		
hsa-miR-34c	323	V\$CRX_Q4	102	14	0.0021092	3.5828	0.3	0.00218		
hsa-miR-328	189	V\$MRF2_01	136	12	0.0021167	3.234	0.3	0.00218		TFs unmapped
hsa-miR-92	383	V\$RFX_Q6	51	10	0.0021184	3.5727	0.3	0.00218	V\$RFX1_01==>hsa-miR-92 in cluster12_hsa-mir-92b	hsa-miR-92==> TF cluster 251: V\$EFC_Q6, V\$RFX1_01, V\$RFX1_02, V\$RFX_Q6, (NM_002918)
hsa-miR-92	383	V\$AHRARNT_02	35	8	0.0021203	3.7629	0.3	0.00218		
hsa-miR-149	193	V\$LEF1_Q6	99	10	0.0021232	3.962	0.3	0.00218		TFs unmapped
hsa-miR-	299	V\$FRE	147	17	0.00213	3.386	0.3	0.00218		

152		AC2_01			03					
hsa-miR-371	18	V\$ZF5_B	82	3	0.0021472	5.7359	0.3	0.00218		TFs unmapped
hsa-miR-19b	489	V\$ATF4_Q2	28	8	0.0021514	4.4206	0.3	0.00218		
hsa-miR-128b	474	V\$FOX_O3_01	94	17	0.0021578	3.1755	0.3	0.00218	V\$FOX_Q2==>hsa-miR-128b in cluster176_hsa-mir-128b	
hsa-miR-130b	441	V\$MRF2_01	136	21	0.0021712	3.4355	0.3	0.00218		TFs unmapped
hsa-miR-29a	483	V\$GAT_A1_04	77	15	0.0021829	3.3551	0.3	0.00218		

Table 8: miR-TF significantly co-occurring pairs in the PicTar network, 5kb promoters.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value <10E-3 in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfbsConsFactors track.

The Network of miR-TF Coregulation Reveals Recurring Local Architectures - Network Motifs

It was suggested that in circuits composed of a miR and a TF, in which these two regulators target the same genes, the TF may also exert a regulatory effect on the miR with which it coregulates the target genes [Hornstein E, Shomron N (2006) Nat Genet 38 Suppl: S20-S24]. It was suggested that such a feed-forward loop (FFL), a well known local feature of many biological networks, may have a beneficial function. An FLL consisting of a TF and a miR could act as a switch for developmental and other programs in cells, since it may acquire biological systems with robustness to noise by means of canalization of perturbations. The present inventors wanted to check whether in any of the significant miR-TF partners discovered above, the miR and its partner TF may regulate each other. Accordingly, the present inventors determined how many of the TF-miR partner pairs (out of 104 pairs in the TargetScan dataset and 916 pairs in the PicTar dataset) had a conserved TF binding site of the partner TF, in the putative upstream regulatory region of the partner

miR (see Materials and Methods for definition of miRs' up-stream putative regulatory regions). Interestingly, it was found that ten of the TF-miR pairs in the TargetScan dataset (9.6 % of the pairs), and 75 out of 916 pairs in the PicTar dataset (8.2 %) fulfilled that additional requirement (see Figure 4). To establish whether this rate was significant, a randomization test was carried out (see Materials and Methods) in which the present inventors computed, in 10,000 randomized sets of TF-miR pairs, the rate of formation of a regulatory interaction between the TF and the miR. In the TargetScan network a modest p -value of 0.024 was obtained, however in both PicTar networks the present inventors obtained the minimal possible p -value, $<10^{-4}$, i.e., in all 10,000 randomizations a rate of direct regulatory interaction between a TF and the miR was obtained, which was lower than the to the original data (see corresponding z-scores in Figure 4). Thus, the cases in which a TF and a miR co-occur in a highly significant number of target genes was associated more often than random with a direct regulation between the TF and the miR's promoter. This motif was named "FFL TF→miR". The significance of this motif is robust to "noise" in the input, assessed by the method originally used for network motifs in *Escherichia coli* [Shen-Orr SS, et al., 2002 Nat Genet 31: 64-68] (see Materials and Methods).

The present inventors were also interested in the opposite interaction — i.e., the case in which the miR regulates its partner TF. This was named "FFL miR→TF." The present inventors determined how many of the TF-miR partners had a predicted binding site of the partner miR in the 3' UTR of the partner TF; it occurred five times in the TargetScan network, and 42 and 48 times in the PicTar networks, using two cutoffs on gene regulatory region lengths. This rate was not significant in the TargetScan network (p -value = 0.16), yet it was significant in the PicTar networks (p -values 0.0038 and $<10^{-4}$). Interestingly, a composite loop network motif was also found, which was termed "FFL miR↔TF", in which the pair of partners regulate each other, to be significantly over-represented in the PicTar network; it appeared seven times in the PicTar network (see Figure 4).

Information on FFLs is summarized herein below in Tables 9-12.

Table 9

mi R	t a r g e t	TF	targ et num	inter secti on size	hype r- geo metr ic co-	Z- sco re	sig nifi can t FD	corres pondi ng FDR p-val	network motifs - FFLs	
									TF -> miR	miR->TF

	n u m				occu ranc e p- valu e		R lev el (q- val ue)		i R	
mi R- 14 2- 5p	3 1 9	V\$ GA TA 1_0 5	141	22	1.99 E-05	4.0 94	0.1	3.48E- 05	V\$GATA1_05==> miR-142-5p in cluster cluster113_hsa-mir- 142	
mi R- 7	2 0 9	V\$ CD P_0 2	262	24	5.62 E-05	4.9 83	0.2	0.0002 1675	V\$CDPCR3_01,V\$ CDP_01,V\$CDP_0 2==>miR-7 in cluster cluster267_hsa- mir-7-1	
mi R- 10	1 1 6	V\$I RF 2_0 1	146	12	5.64 E-05	5.4 582	0.2	0.0002 1675	V\$IRF2_01==>miR -10 in cluster cluster111_hsa-mir- 10a	
mi R- 93	3 0 5	V\$ E2 F_ Q3 _01	9	5	5.65 E-05	7.2 658	0.2	0.0002 1675	V\$E2F_01,V\$E2F_ 03==>miR-93 in cluster cluster238_hsa-mir- 106b	
mi R- 36 9- 3p	2 9 5	V\$ GA TA _C	98	16	6.28 E-05	4.3 958	0.2	0.0002 1675		miR-369-3p==> TF cluster 110: V\$GATA3_01, V\$GATA_C, (NM_002051)
mi R- 50 3	2 0 2	V\$ CD PC R1 _01	87	12	7.69 E-05	4.2 765	0.2	0.0002 1675	V\$CDP_02==>miR -503 in cluster cluster293_hsa-mir- 424	
mi R- 30	5 7 0	V\$I RF _Q _6	154	32	0.00 01	2.9 862	0.2	0.0002 1675		miR-30==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
mi R- 10	1 1 6	V\$ PO U6 F1_ 01	261	16	0.00 0116	5.4 943	0.2	0.0002 1675	V\$POU6F1_01==> miR-10 in cluster cluster111_hsa-mir- 10a V\$POU6F1_01==> miR-10 in cluster cluster146_hsa-mir- 10b	TFs unmapped
mi R- 22 1	1 7 6	V\$ FO X_ Q2	112	12	0.00 0241	4.4 253	0.3	0.0005 8879		miR-221==> TF cluster 83: V\$FOX_Q2, (NM_002158)
mi R- 14 8	2 9 2	V\$ FO X_ Q2	112	16	0.00 0281	4.6 302	0.3	0.0005 8879		miR-148==> TF cluster 83: V\$FOX_Q2, (NM_004514)

miR-22	195	V\$SRF_Q4	28	6	0.000386	4.6782	0.3	0.00058879		miR-22==> TF cluster 267: V\$SRF_Q1, V\$SRF_Q4, V\$SRF_Q5_Q1, V\$SRF_Q5_Q2, V\$SRF_Q6, (NM_003131)
miR-93	305	V\$PR_Q2	51	10	0.000438	5.5509	0.3	0.00058879	V\$PR_Q1==>miR-93 in cluster cluster238_hsa-mir-106b	TFs unmapped
miR-505	191	V\$HNF6_Q6	349	25	0.00046	3.7077	0.3	0.00058879	V\$HNF6_Q6==>miR-505 in cluster cluster295_hsa-mir-505	
miR-130	337	V\$NFY_C	144	20	0.000511	3.3669	0.3	0.00058879	V\$ALPHACP1_Q1==>miR-130 in cluster cluster41_hsa-mir-130a V\$ALPHACP1_Q1, V\$NFY_Q1==>miR-130 in cluster cluster170_hsa-mir-130b	
miR-183	186	V\$SOX_Q6	84	10	0.000531	3.8729	0.3	0.00058879	V\$SOX_Q6==>miR-183 in cluster cluster242_hsa-mir-183	

Table 9 - miR-TF FFLs in the TargetScan network.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value <10E-3 in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfsConsFactors track.

Table 10

miR	target	TF	target num	intersection size	hyper-geometric co-occurrence p-	Z-score	significant FDR level (q-	corresponding FDR p-val	network motifs - FFLs	
									TF->miR	miR->TF

	n u m			e	value		value)			
hsa-miR-199b	190	V\$TCF11M AFG_01	164	19	4.21E-07	5.6021	0.1	0.00038368		hsa-miR-199b==> TF cluster 162: V\$MAF_Q6_01, V\$TCF11M AFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-142-5p	284	V\$GATA1_05	166	23	1.34E-06	5.1857	0.1	0.00038368	V\$GATA1_05==>hsa-miR-142-5p in cluster cluster113_hsa-mir-142	
hsa-miR-10a	131	V\$POU6F1_01	302	20	3.74E-06	5.4437	0.1	0.00038368	V\$POU6F1_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a	TFs unmapped
hsa-miR-10b	131	V\$POU6F1_01	302	20	3.74E-06	6.0644	0.1	0.00038368	V\$POU6F1_01==>hsa-miR-10b in cluster cluster146_hsa-mir-10b	TFs unmapped
hsa-miR-218	417	V\$CDP_R1_01	89	19	4.31E-06	5.8815	0.1	0.00038368	V\$CDP_01==>hsa-miR-218 in cluster cluster216_hsa-mir-218-2	
hsa-miR-199a	151	V\$PAX_Q6	121	13	5.80E-06	5.234	0.1	0.00038368	V\$PAX_Q6==>hsa-miR-199a in cluster cluster128_hsa-mir-199a-1	
hsa-miR-30b	624	V\$IRF_Q6	170	36	7.98E-06	4.089	0.1	0.00038368		hsa-miR-30b==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)
hsa-miR-30c	624	V\$IRF_Q6	170	36	7.98E-06	4.3065	0.1	0.00038368		hsa-miR-30c==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_01, (NM_002460)

										0)
hsa-miR-199a	1 5 1	V\$T CF1 1M AFG _01	16 4	15	8.12E-06	4.9904	0.1	0.00038 368		hsa-miR-199a==> TF cluster 162: V\$MAF_Q6_01, V\$TCF11M AFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-30a-5p	6 2 5	V\$I RF_ Q6	17 0	36	8.27E-06	4.271	0.1	0.00038 368		hsa-miR-30a-5p==> TF cluster 152: V\$I RF_Q6, V\$I RF_Q6_01, (NM_002460)
hsa-miR-30d	6 2 6	V\$I RF_ Q6	17 0	36	8.58E-06	4.5803	0.1	0.00038 368		hsa-miR-30d==> TF cluster 152: V\$I RF_Q6, V\$I RF_Q6_01, (NM_002460)
hsa-miR-28	1 2 4	V\$A P1_ Q2_ _01	71	9	9.28E-06	5.5825	0.1	0.00038 368	V\$AP1_Q2_01==>hsa-miR-28 in cluster cluster191_hsa-mir-28	
hsa-miR-30e-5p	6 2 9	V\$I RF_ Q6	17 0	36	9.56E-06	3.6723	0.1	0.00038 368		hsa-miR-30e-5p==> TF cluster 152: V\$I RF_Q6, V\$I RF_Q6_01, (NM_002460)
hsa-miR-23a	3 9 1	V\$T GIF _01	10 1	18	4.30E-05	4.4038	0.1	0.00038 368		hsa-miR-23a==> TF cluster 291: V\$TGIF_01, (NM_003244)
hsa-miR-23b	3 9 5	V\$T GIF _01	10 1	18	4.92E-05	4.1178	0.1	0.00038 368		hsa-miR-23b==> TF cluster 291: V\$TGIF_01, (NM_003244)
hsa-miR-194	1 8 6	V\$F OX_ Q2	14 0	14	6.26E-05	3.8321	0.1	0.00038 368		hsa-miR-194==> TF cluster 96:

										V\$FOXO1_02, V\$FOX_Q2, (NM_002015)
hsa-miR-198	250	V\$ZID_01	92	13	6.40E-05	4.6917	0.1	0.00038368	V\$ZID_01==>hsa-miR-198 in cluster cluster187_hsa-mir-198	
hsa-miR-182	501	V\$FREAC2_01	217	34	9.64E-05	3.4548	0.1	0.00038368	hsa-miR-182==> TF cluster 87: V\$FOX_Q2, V\$FREAC2_01, (NM_001452)	
hsa-miR-10a	131	V\$IRF2_01	157	12	9.79E-05	4.9299	0.1	0.00038368	V\$IRF2_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a	
hsa-miR-23a	391	V\$IRF_Q6	170	24	0.0001265	3.5698	0.1	0.00038368	hsa-miR-23a==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-23a==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_01, (NM_002198 NM_002199)	
hsa-miR-302c-star	343	V\$OCT1_01	159	21	0.00013963	3.7483	0.1	0.00038368	V\$OCT1_06==>hsa-miR-302c-star in cluster cluster201_hsa-mir-302b	
hsa-miR-23b	395	V\$IRF_Q6	170	24	0.00014806	3.395	0.1	0.00038368	hsa-miR-23b==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-23b==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_01	

										01, (NM_00219 8 NM_002199)
hsa-miR-193a	1 7 4	V\$C DPC R1_ 01	89	10	0.0001 6161	4.5398	0.1	0.00038 368	V\$CDPCR3 HD_01==>hs a-miR-193a in cluster cluster107_hs a-mir-193a	
hsa-miR-30c	6 2 4	V\$ MEF 2_03	78	19	0.0001 6887	3.8289	0.1	0.00038 368	V\$HMEF2_ Q6==>hsa- miR-30c in cluster cluster5_hsa- mir-30e	
hsa-miR-30e-5p	6 2 9	V\$ MEF 2_03	78	19	0.0001 8761	3.476	0.1	0.00038 368	V\$HMEF2_ Q6==>hsa- miR-30e-5p in cluster cluster5_hsa- mir-30e	
hsa-miR-204	2 9 9	V\$ MEF 2_04	16 3	19	0.0002 5495	4.1189	0.1	0.00038 368	V\$MEF2_01 ==>hsa-miR- 204 in cluster cluster266_hs a-mir-204	
hsa-miR-148b	3 2 1	V\$F OX_ Q2	14 0	18	0.0002 5927	3.3973	0.1	0.00038 368	hsa-miR- 148b==> TF cluster 83: V\$FOX_Q2, (NM_00451 4)	
hsa-miR-200b	4 4 0	V\$O CT1 01	15 9	24	0.0002 6898	3.0977	0.1	0.00038 368	V\$OCT1_Q6 ==>hsa-miR- 200b in cluster cluster1_hsa- mir-200b	
hsa-miR-93	5 4 1	V\$P PAR A_0 2	65	15	0.0003 2559	4.4361	0.1	0.00038 368	V\$DR4_Q2, V\$PPARA_0 2==>hsa- miR-93 in cluster cluster238_hs a-mir-106b	hsa-miR- 93==> TF cluster 229: V\$PPARA_ 01, V\$PPARA_ 02, V\$PPAR_D R1_Q2, (NM_00503 6)
hsa-miR-153	3 5 9	V\$H NF6 Q6	40 3	40	0.0003 8368	3.2026	0.1	0.00038 368	V\$HNF6_Q6 ==>hsa-miR- 153 in cluster cluster247_hs a-mir-153-2	
hsa-miR-10a	1 3 1	V\$I RF7 01	18 2	12	0.0003 9286	4.5929	0.2	0.00170 8	V\$IRF7_01= =>hsa-miR- 10a in cluster	

									cluster111_hs a-mir-10a	
hsa- miR- 130b	4 7 4	V\$N FY_ C	16 1	25	0.0004 0387	3.2246	0.2	0.00170 8	V\$ALPHAC P1_01,V\$NF Y_01==>hsa- miR-130b in cluster cluster170_hs a-mir-130b	
hsa- miR- 183	2 1 9	V\$S OX5 _01	96	11	0.0004 8042	3.6473	0.2	0.00170 8	V\$SOX_Q6= =>hsa-miR- 183 in cluster cluster242_hs a-mir-183	
hsa- miR- 30a- 3p	2 2 6	V\$O CT_ Q6	28 2	22	0.0004 884	3.2705	0.2	0.00170 8	V\$POU3F2_ 01==>hsa- miR-30a-3p in cluster cluster224_hs a-mir-30a	hsa-miR- 30a-3p==> TF cluster 215: V\$OCT_Q6, (NM_00623 7)
hsa- miR- 30e- 3p	2 2 6	V\$O CT_ Q6	28 2	22	0.0004 884	3.2711	0.2	0.00170 8		hsa-miR- 30e-3p==> TF cluster 215: V\$OCT_Q6, (NM_00623 7)
hsa- miR- 142- 3p	1 5 2	V\$Y Y1_ 02	16 1	12	0.0005 0154	3.8084	0.2	0.00170 8	V\$YY1_02= =>hsa-miR- 142-3p in cluster cluster113_hs a-mir-142	
hsa- miR- 15b	5 9 2	V\$C DPC R1_ 01	89	19	0.0005 2239	3.4899	0.2	0.00170 8	V\$CDP_02= =>hsa-miR- 15b in cluster cluster188_hs a-mir-15b	
hsa- miR- 32	4 4 4	V\$E TS_ Q4	16	6	0.0005 3333	4.1619	0.2	0.00170 8		hsa-miR- 32==> TF cluster 72: V\$ETS_Q4, (NM_00201 7)
hsa- miR- 93	5 4 1	V\$I RF_ Q6	17 0	28	0.0005 9713	3.1772	0.2	0.00170 8		hsa-miR- 93==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_ 01, hsa- miR-93==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_ 01,

										(NM_002198 NM_002199)
hsa-miR-137	360	V\$N KX2 5_02	331	34	0.0006 0644	2.7626	0.2	0.00170 8	V\$NKKX25_02=>hsa-miR-137 in cluster cluster8_hsa-mir-137	TFs unmapped
hsa-miR-130a	488	V\$N FY_ C	161	25	0.0006 2412	3.5499	0.2	0.00170 8	V\$ALPHAC P1_01=>hsa-miR-130a in cluster cluster41_hsa-mir-130a	
hsa-miR-93	541	V\$P R_0 2	76	16	0.0006 2607	3.6701	0.2	0.00170 8	V\$PR_01=>hsa-miR-93 in cluster cluster238_hsa-mir-106b	TFs unmapped
hsa-miR-367	346	V\$F OX_ Q2	140	18	0.0006 4215	3.5483	0.2	0.00170 8	V\$FOXO4_02=>hsa-miR-367 in cluster cluster201_hsa-mir-302b	hsa-miR-367=> TF cluster 83: V\$FOX_Q2, (NM_002158)
hsa-miR-96	544	V\$C REB_ Q2	98	19	0.0006 4372	2.9232	0.2	0.00170 8	V\$CREB_Q2_01=>hsa-miR-96 in cluster cluster242_hsa-mir-183	hsa-miR-96=> TF cluster 46: V\$CREBAT F_Q6, V\$CREB_01, V\$CREB_02, V\$CREB_Q2, V\$CREB_Q2_01, V\$CREB_Q4, V\$CREB_Q4_01, V\$TAXCREB_01, V\$TAXCREB_02, (NM_004379)
hsa-miR-367	346	V\$P OU3 F2_0 1	201	23	0.0006 543	3.4002	0.2	0.00170 8	V\$POU3F2_01=>hsa-miR-367 in cluster cluster201_hsa-mir-302b	
hsa-miR-217	171	V\$C DPC R1_ 01	89	9	0.0006 6703	3.7563	0.2	0.00170 8	V\$CDP_02=>hsa-miR-217 in cluster cluster143_hsa	

									a-mir-216	
hsa-miR-32	4 4 4	V\$FOX OX O4_ 01	36	9	0.0007 0029	4.9641	0.2	0.00170 8	V\$FOXO4_0 2==>hsa- miR-32 in cluster cluster270_hs a-mir-32	
hsa-miR-122a	1 1 6	V\$DEC EC_ Q1	59	6	0.0007 1919	5.1785	0.2	0.00170 8	hsa-miR-122a==> TF cluster 23: V\$DEC_Q1, (NM_030762)	
hsa-miR-194	1 8 6	V\$TGIF GIF 01	10 1	10	0.0007 7374	3.7789	0.2	0.00170 8	hsa-miR-194==> TF cluster 291: V\$TGIF_Q1, (NM_003244)	
hsa-miR-181a	4 7 6	V\$SETS TS_ Q4	16	6	0.0007 7499	4.0731	0.2	0.00170 8	hsa-miR-181a==> TF cluster 72: V\$SETS_Q4, hsa-miR-181a==> TF cluster 308: V\$SETS1_B, V\$SETS_Q4, (NM_005238)	
hsa-miR-181c	4 7 6	V\$SETS TS_ Q4	16	6	0.0007 7499	4.2919	0.2	0.00170 8	hsa-miR-181c==> TF cluster 72: V\$SETS_Q4, hsa-miR-181c==> TF cluster 308: V\$SETS1_B, V\$SETS_Q4, (NM_005238)	
hsa-miR-196a	1 3 6	V\$SS 8_01	13 8	10	0.0007 8161	3.8071	0.2	0.00170 8	TFs unmapped	
hsa-miR-181b	4 7 7	V\$SETS TS_ Q4	16	6	0.0007 8373	4.0559	0.2	0.00170 8	hsa-miR-181b==> TF cluster 72: V\$SETS_Q4, hsa-miR-181b==> TF cluster 308: V\$SETS1_B, V\$SETS_Q4, (NM_005238)	
hsa-miR-146b	1 0 6	V\$STAT TAT 5A_	91	7	0.0008 2359	4.4518	0.2	0.00170 8	V\$STAT_Q1, V\$STAT_Q6 ==>hsa-miR-	

		01							146b in cluster34_hsa-mir-146b	
hsa-miR-19b	520	V\$PAX6_Q2	121	21	0.00086557	3.421	0.2	0.001708	V\$PAX_Q6==>hsa-miR-19b in cluster292_hsa-mir-106a	
hsa-miR-136	128	V\$EVII_06	124	9	0.00092114	4.1542	0.2	0.001708	V\$EVII_04==>hsa-miR-136 in cluster77_hsa-mir-493	TFs unmapped
hsa-miR-150	181	V\$MYB_Q5_01	16	4	0.00093628	4.4512	0.2	0.001708	hsa-miR-150==> TF cluster 312: V\$CMYB_01, V\$MYB_Q3, V\$MYB_Q5_01, V\$MYB_Q6, (NM_005375)	
hsa-miR-10a	131	V\$AIRE_02	201	12	0.00095639	4.1956	0.2	0.001708	V\$AIRE_02==>hsa-miR-10a in cluster111_hsa-mir-10a	
hsa-miR-34b	246	V\$EVII_01	170	16	0.00098273	3.6	0.2	0.001708	V\$EVII_03==>hsa-miR-34b in cluster47_hsa-mir-34b	TFs unmapped
hsa-miR-9-star	300	V\$FOX_P1_01	195	20	0.00098552	2.958	0.2	0.001708	V\$FOX_P1_01==>hsa-miR-9-star in cluster209_hsa-mir-9-2	TFs unmapped
hsa-miR-219	173	V\$PPARG_01	93	9	0.00099889	3.763	0.2	0.001708	V\$PPARG_02==>hsa-miR-219 in cluster220_hsa-mir-219-1	TFs unmapped
hsa-miR-16	577	V\$CDP_R1_01	89	18	0.0010508	3.3513	0.2	0.001708	V\$CDP_02==>hsa-miR-16 in cluster188_hsa-mir-15b	
hsa-miR-23a	391	V\$RFX_Q6	79	13	0.0010861	3.5127	0.2	0.001708	V\$RFX1_02==>hsa-miR-23a in cluster129_hsa-mir-23a	

hsa-miR-195	585	V\$OCT1_03	54	13	0.0010964	3.2971	0.2	0.001708	V\$OCT1_01==>hsa-miR-195 in cluster cluster102_hsa-mir-497	
hsa-miR-132	191	V\$AP1_Q4	41	6	0.0013754	3.2858	0.2	0.001708	V\$AP1_01,V\$AP1_Q4==>hsa-miR-132 in cluster cluster101_hsa-mir-212	TFs unmapped
hsa-miR-212	191	V\$AP1_Q4	41	6	0.0013754	3.3562	0.2	0.001708	V\$AP1_01,V\$AP1_Q4==>hsa-miR-212 in cluster cluster101_hsa-mir-212	TFs unmapped
hsa-miR-182	501	V\$SOX5_01	96	17	0.0014007	3.0415	0.2	0.001708	V\$SOX_Q6==>hsa-miR-182 in cluster cluster242_hsa-mir-183	hsa-miR-182==> TF cluster 280: V\$SOX5_01, V\$SOX_Q6, (NM_006940)
hsa-miR-130a	488	V\$SOX_Q6	152	23	0.0014578	2.838	0.2	0.001708		hsa-miR-130a==> TF cluster 279: V\$SOX_Q6, hsa-miR-130a==> TF cluster 280: V\$SOX5_01, V\$SOX_Q6, (NM_003107 NM_006940 NM_007084)
hsa-miR-326	261	V\$OCT1_06	107	12	0.0015498	3.0782	0.2	0.001708	V\$OCT_C==>hsa-miR-326 in cluster cluster46_hsa-mir-326	
hsa-miR-93	541	V\$E2F_Q3_01	7	4	0.0015613	6.3707	0.2	0.001708	V\$E2F_01,V\$E2F_Q3==>hsa-miR-93 in cluster cluster238_hsa-mir-106b	hsa-miR-93==> TF cluster 58: V\$E2F1_Q3_01, V\$E2F1_Q4, V\$E2F1_Q4_01, V\$E2F1_Q6, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02,

									V\$E2F_03, V\$E2F_Q3_ 01, V\$E2F_Q4_ 01, V\$E2F_Q6_ 01, hsa- miR-93==> TF cluster 62: V\$E2F1_Q4_ 01, V\$E2F_02, V\$E2F_Q3_ 01, V\$E2F_Q4_ 01, V\$E2F_Q6_ 01, (NM_00194 9 NM_005225)
hsa- miR- 302c -star	3 4 3	V\$O CT_ C	29 7	29	0.0015 867	2.6684	0.2	0.00170 8	V\$OCT1_06 ==>hsa-miR- 302c-star in cluster cluster201_hsa- mir-302b
hsa- miR- 196a	1 3 6	V\$ MM EF2 Q6	15 2	10	0.0016 39	3.6515	0.2	0.00170 8	V\$MEF2_03 ==>hsa-miR- 196a in cluster cluster53_hsa- mir-196a-2
hsa- miR- 26a	4 6 5	V\$P BX1 01	87	15	0.0016 596	3.3877	0.2	0.00170 8	V\$PBX_Q3= =>hsa-miR- 26a in cluster cluster57_hsa- mir-26a-2 TFs unmapped
hsa- miR- 129	2 0 4	V\$F OXJ 2_02	30 0	20	0.0017 18	3.3104	0.3	0.00520 27	V\$FOXJ2_01 ,V\$FOXJ2_0 2==>hsa- miR-129 in cluster cluster40_hsa- mir-129-2 V\$FOXJ2_02 ==>hsa-miR- 129 in cluster cluster241_hsa- mir-129-1
hsa- miR- 22	2 6 5	V\$C MY B_0 1	54	8	0.0017 727	4.2956	0.3	0.00520 27	V\$MYB_Q3 ==>hsa-miR- 22 in cluster cluster100_hsa- mir-22

hsa-miR-372	560	V\$E2F_Q3_01	7	4	0.0017792	5.7473	0.3	0.0052027	hsa-miR-372==> TF cluster 58: V\$E2F1_Q3_01, V\$E2F1_Q4_01, V\$E2F1_Q6_01, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02, V\$E2F_03, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-372==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949 NM_005225)
hsa-miR-218	417	V\$S8_01	138	19	0.0018561	3.0214	0.3	0.0052027	V\$S8_01==> hsa-miR-218 in cluster cluster216_hsa-mir-218-2 TFs unmapped
hsa-miR-204	299	V\$AMEF2_Q6	206	20	0.0018569	3.0993	0.3	0.0052027	V\$MEF2_01==> hsa-miR-204 in cluster cluster266_hsa-mir-204
hsa-miR-19b	520	V\$POU6F1_01	302	40	0.0018686	2.5878	0.3	0.0052027	V\$POU6F1_01==> hsa-miR-19b in cluster cluster292_hsa-mir-106a TFs unmapped
hsa-miR-92	413	V\$TST1_01	150	20	0.0018797	3.2522	0.3	0.0052027	V\$TST1_01==> hsa-miR-92 in cluster cluster292_hsa-mir-106a
hsa-	2	V\$T	10	11	0.0019	3.7093	0.3	0.00520	hsa-miR-

miR-323	4 6	GIF_01	1		14			27		323==> TF cluster 291: V\$TGIF_01, (NM_003244)
hsa-miR-1	4 0 2	V\$OCT1_03	54	10	0.0019856	3.2242	0.3	0.0052027	V\$OCT1_B==>hsa-miR-1 in cluster cluster122_hsa-mir-1-2	
hsa-miR-342	1 4 3	V\$TGIF_01	10 1	8	0.0020541	3.5151	0.3	0.0052027	hsa-miR-342==> TF cluster 291: V\$TGIF_01, (NM_003244)	
hsa-miR-138	3 9 4	V\$DR4_Q2	94	14	0.0020615	3.5207	0.3	0.0052027	hsa-miR-138==> TF cluster 248: V\$DR4_Q2, hsa-miR-138==> TF cluster 259: V\$DR3_Q4, V\$DR4_Q2, V\$PPARA_02, (NM_000964 NM_002957)	
hsa-miR-302a	3 4 2	V\$P53_01	85	12	0.0020692	3.3715	0.3	0.0052027		
hsa-miR-101	4 2 9	V\$NRF2_Q4	15 6	21	0.0020705	2.7525	0.3	0.0052027	hsa-miR-101==> TF cluster 214: V\$MAF_Q6_01, V\$NRF2_Q4, (NM_006164)	
hsa-miR-30e-3p	2 2 6	V\$MEF2_04	16 3	14	0.0021653	3.358	0.3	0.0052027	V\$HMEF2_Q6==>hsa-miR-30e-3p in cluster cluster5_hsa-mir-30e	
hsa-miR-372	5 6 0	V\$IRF_Q6	17 0	27	0.0021745	2.7418	0.3	0.0052027	hsa-miR-372==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_01, hsa-miR-372==> TF cluster 151: V\$IRF2_01,	

										V\$IRF_Q6, V\$IRF_Q6_ 01, (NM_00219 8 NM_002199)
hsa- miR- 222	2 0 8	V\$S RF_ Q6	87	9	0.0022 493	3.1038	0.3	0.00520 27	V\$SRF_01,V \$SRF_Q6== >hsa-miR- 222 in cluster cluster280_hs a-mir-222	
hsa- miR- 328	2 0 7	V\$E RR1 _Q2	56	7	0.0022 848	3.9833	0.3	0.00520 27	hsa-miR- 328==> TF cluster 73: V\$ERR1_Q 2, (NM_00445 1)	
hsa- miR- 302a	3 4 2	V\$P AX6 _Q2	12 1	15	0.0022 98	2.916	0.3	0.00520 27	V\$PAX6_01 ==>hsa-miR- 302a in cluster cluster201_hs a-mir-302b	
hsa- miR- 133a	3 1 8	V\$O CT1 _04	93	12	0.0024 432	3.2997	0.3	0.00520 27	V\$OCT1_B= =>hsa-miR- 133a in cluster cluster122_hs a-mir-1-2	
hsa- miR- 205	2 4 2	V\$C EBP B_0 I	49	7	0.0025 323	4.0139	0.3	0.00520 27	V\$CEBPB_0 1,V\$CEBP_ Q3==>hsa- miR-205 in cluster cluster22_hs a-mir-205	
hsa- miR- 302d	3 4 6	V\$P AX6 _Q2	12 1	15	0.0025 721	2.984	0.3	0.00520 27	V\$PAX6_01 ==>hsa-miR- 302d in cluster cluster201_hs a-mir-302b	
hsa- miR- 302c	3 1 2	V\$P AX6 _Q2	12 1	14	0.0026 193	2.8657	0.3	0.00520 27	V\$PAX6_01 ==>hsa-miR- 302c in cluster cluster201_hs a-mir-302b	
hsa- miR- 96	5 4 4	V\$A HR_ 01	71	14	0.0027 342	3.0491	0.3	0.00520 27	V\$AHRARN T_02,V\$AH R_01==>hsa- miR-96 in cluster cluster242_hs a-mir-183	

hsa-miR-221	2 1 7	V\$SRF_Q6	87	9	0.0029 969	3.3545	0.3	0.00520 27	V\$SRF_01,V\$SRF_Q6=>hsa-miR-221 in cluster cluster280_hsa-mir-222	
hsa-miR-330	3 4 3	V\$CDPCR3_R1_01	89	12	0.0031 431	3.0721	0.3	0.00520 27	V\$CDPCR3_01=>hsa-miR-330 in cluster cluster134_hsa-mir-330	
hsa-miR-32	4 4 4	V\$RFX_Q6	79	13	0.0033 869	3.3759	0.3	0.00520 27	hsa-miR-32=> TF cluster 251: V\$EFC_Q6, V\$RFX1_01, V\$RFX1_02, V\$RFX_Q6, (NM_002918)	
hsa-miR-218	4 1 7	V\$POU3F2_01	20 1	24	0.0035 766	2.3801	0.3	0.00520 27	hsa-miR-218=> TF cluster 226: V\$BRN2_01, V\$OCT_Q6, V\$POU3F2_01, V\$POU3F2_02, hsa-miR-218=> TF cluster 227: V\$POU3F2_01, V\$POU3F2_02, (NM_005604)	
hsa-miR-193b	1 7 1	V\$E2F_Q4_01	12	3	0.0036 723	5.5816	0.3	0.00520 27	hsa-miR-193b=> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949)	
hsa-let-7f	4 9 4	V\$ETS1_B	72	13	0.0036 943	2.8659	0.3	0.00520 27	hsa-let-7f=> TF cluster 308: V\$ETS1_B,	

										V\$ETS_Q4, (NM_00523 8)
hsa- miR- 181c	4 7 6	V\$C DP_ 01	19 7	26	0.0037 541	2.6685	0.3	0.00520 27	V\$CDP_01= =>hsa-miR- 181c in cluster cluster130_hs a-mir-181c	
hsa- miR- 21	1 3 5	V\$I RF1 01	49	5	0.0038 549	4.1659	0.3	0.00520 27	V\$IRF_Q6== >hsa-miR-21 in cluster cluster115_hs a-mir-21	
hsa- miR- 193a	1 7 4	V\$E 2F_ Q4_ 01	12	3	0.0038 575	5.0486	0.3	0.00520 27	hsa-miR- 193a==> TF cluster 62: V\$E2F1_Q4 _01, V\$E2F_02, V\$E2F_Q3_ 01, V\$E2F_Q4_ 01, V\$E2F_Q6_ 01, (NM_00194 9)	
hsa- miR- 219	1 7 3	V\$P R_Q 2	24	4	0.0038 813	3.6116	0.3	0.00520 27	V\$PR_01,V\$ PR_Q2==>hs a-miR-219 in cluster cluster220_hs a-mir-219-1	
hsa- miR- 125b	3 7 0	V\$E TS2 _B	64	10	0.0039 629	3.5117	0.3	0.00520 27	V\$ETS2_B= =>hsa-miR- 125b in cluster cluster48_hsa -mir-125b-1	
hsa- miR- 302d	3 4 6	V\$S P3_ Q3	80	11	0.0042 295	2.9586	0.3	0.00520 27	hsa-miR- 302d==> TF cluster 282: V\$SP3_Q3, (NM_00311 1)	
hsa- miR- 129	2 0 4	V\$S P3_ Q3	80	8	0.0042 901	3.1032	0.3	0.00520 27	hsa-miR- 129==> TF cluster 282: V\$SP3_Q3, (NM_00311 1)	
hsa- miR- 92	4 1 3	V\$F OXP 1_01	19 5	23	0.0044 546	2.4583	0.3	0.00520 27	V\$FOXP1_0 1==>hsa- miR-92 in cluster cluster292_hs a-mir-106a	TFs unmapped
hsa-	3	V\$S	15	16	0.0046	2.7661	0.3	0.00520		hsa-miR-

miR-148b	2 1	OX_ Q6	2		622			27		148b==> TF cluster 280: V\$SOX5_0 1, V\$SOX_Q6, (NM_00694 0)
hsa-miR-7	2 5 2	V\$ MEF 2_01	21 1	17	0.0047 42	2.8406	0.3	0.00520 27	V\$MEF2_04 ==>hsa-miR- 7 in cluster cluster267_hs a-mir-7-1	
hsa-miR-199a	1 5 1	V\$S RF_ Q6	87	7	0.0048 121	3.1521	0.3	0.00520 27	V\$SRF_C== >hsa-miR- 199a in cluster cluster17_hsa -mir-199a-2 V\$SRF_Q5_ 01==>hsa- miR-199a in cluster cluster128_hs a-mir-199a-1	
hsa-miR-195	5 8 5	V\$T CF1 IM AFG _01	16 4	26	0.0048 33	2.6177	0.3	0.00520 27	hsa-miR- 195==> TF cluster 162: V\$MAF_Q6 _01, V\$TCF11M AFG_01, V\$TCF11_0 1, (NM_00320 4)	
hsa-miR-15a	5 8 5	V\$T CF1 IM AFG _01	16 4	26	0.0048 33	2.7684	0.3	0.00520 27	hsa-miR- 15a==> TF cluster 162: V\$MAF_Q6 _01, V\$TCF11M AFG_01, V\$TCF11_0 1, (NM_00320 4)	
hsa-miR-199a	1 5 1	V\$P AX2 _01	66	6	0.0049 177	3.6369	0.3	0.00520 27	V\$PAX_Q6= =>hsa-miR- 199a in cluster cluster128_hs a-mir-199a-1	
hsa-miR-152	3 2 3	V\$S OX_ Q6	15 2	16	0.0049 498	2.9903	0.3	0.00520 27	V\$SOX9_B1 ==>hsa-miR- 152 in cluster cluster110_hs a-mir-152	hsa-miR- 152==> TF cluster 280: V\$SOX5_0 1, V\$SOX_Q6, (NM_00694 0)

hsa-miR-129	204	V\$OCT1_07	262	17	0.0049882	2.7065	0.3	0.0052027	V\$OCT_C==>hsa-miR-129 in cluster cluster40_hsa-mir-129-2
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Table 10 - miR-FFLs in the PicTar network, 10kb promoters.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value $<6 \times 10^{-3}$ (FDR q-value=0.3) in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfbsConsFactors track.

Table 11

miR	target num	TF	target num	interaction size	hyper-geometric co-occurrence p-value	Z-score	significant FDR level (q-value)	corresponding FDR p-value	network motifs - FFLs	
									TF->miR	miR->TF
hsa-miR-28	1	V\$AP1_Q2_01	47	9	3.83E-07	6.6543	0.1	9.53E-05	V\$AP1_Q2_01==>hsa-miR-28 in cluster cluster191_hsa-mir-28	
hsa-miR-28	1	V\$OCT1_T1_06	66	9	7.46E-06	6.9642	0.1	9.53E-05	V\$OCT1_01==>hsa-miR-28 in cluster cluster191_hsa-mir-28	
hsa-miR-199b	1	V\$TCF11M1_AFG_01	103	13	1.33E-05	5.3654	0.1	9.53E-05		hsa-miR-199b==> TF cluster 162: V\$MAF_Q6_01, V\$TCF11MAFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-199a	1	V\$PAX3_X6_Q42	73	9	5.49E-05	4.7014	0.1	9.53E-05	V\$PAX_Q6==>hsa-miR-199a in cluster cluster128_hsa-mir-	

hsa-miR-142-5p	2 6 15	V\$GA TAI_0 15	89	14	5.69E-05	4.4576	0.1	9.53E-05	199a-1 V\$GATA1_05==>hsa-miR-142-5p in cluster cluster113_hsa-mir-142	
hsa-miR-93	4 9 5	V\$PR _02 5	49	14	5.89E-05	4.305	0.1	9.53E-05	V\$PR_01==>hsa-miR-93 in cluster cluster238_hsa-mir-106b	TFs unmapped
hsa-miR-10a	1 2 3	V\$PO U6F1_ 01	169	13	7.93E-05	5.2782	0.1	9.53E-05	V\$POU6F1_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a	TFs unmapped
hsa-miR-194	1 8 0	V\$FO X_Q2 0	85	11	7.95E-05	4.9154	0.1	9.53E-05		hsa-miR-194==> TF cluster 96: V\$FOXO1_02, V\$FOX_Q2, (NM_002015)
hsa-miR-302b	2 8 8	V\$NF Y_C 8	139	19	8.45E-05	3.5759	0.1	9.53E-05		hsa-miR-302b==> TF cluster 36: V\$NFY_C, V\$NFY_Q6, V\$NFY_Q6_01, (NM_002505)
hsa-miR-10b	1 2 4	V\$PO U6F1_ 01	169	13	8.63E-05	4.7742	0.1	9.53E-05	V\$POU6F1_01==>hsa-miR-10b in cluster cluster146_hsa-mir-10b	TFs unmapped
hsa-miR-199a	1 3 4	V\$TC F11M AFG_ 01	103	10	0.000165	4.0913	0.2	0.00073		hsa-miR-199a==> TF cluster 162: V\$MAF_Q6_01, V\$TCF11MAFG_01, V\$TCF11_01, (NM_003204)
hsa-miR-200b	4 0 9	V\$OC T1_01 9	97	18	0.0002007	4.424	0.2	0.00073	V\$OCT1_Q6==>hsa-miR-200b in cluster cluster1_hsa-mir-200b	
hsa-miR-30a-5p	5 8 3	V\$AF P1_Q6 3	114	25	0.0002346	3.6755	0.2	0.00073	V\$AFP1_Q6==>hsa-miR-30a-5p in cluster cluster224_hsa-mir-30a	TFs unmapped
hsa-miR-199a-star	3 9 3	V\$FO X_Q2 3	85	16	0.0002417	3.4314	0.2	0.00073	V\$FOXJ2_01,V\$FOX_Q2==>hsa-miR-199a-star in cluster cluster17_hsa-mir-199a-2	
hsa-miR-32	4 1	V\$RF X_Q6	51	12	0.0002642	5.0467	0.2	0.00073		hsa-miR-32==> TF

	3								cluster 251: V\$EFC_Q6, V\$RFX1_01, V\$RFX1_02, V\$RFX_Q6, (NM_002918)
hsa-miR-23a	3 5 5	V\$RF X_Q6	51	11	0.0002 876	5.118 9	0.2	0.00073	V\$RFX1_02==>hsa-miR-23a in cluster cluster129_hsa-mir-23a
hsa-miR-302c-star	3 1 6	V\$OC T1_01	97	15	0.0003 268	3.792 9	0.2	0.00073	V\$OCT1_06==>hsa-miR-302c-star in cluster cluster201_hsa-mir-302b
hsa-miR-302d	3 2 0	V\$NF Y_C	139	19	0.0003 361	3.875 5	0.2	0.00073	hsa-miR-302d==> TF cluster 36: V\$NFY_C, V\$NFY_Q6, V\$NFY_Q6_0 1, (NM_002505)
hsa-miR-30b	5 8 2	V\$IRF _Q6	98	22	0.0003 794	3.792	0.2	0.00073	hsa-miR-30b==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002460)
hsa-miR-30c	5 8 2	V\$IRF _Q6	98	22	0.0003 794	3.781 5	0.2	0.00073	hsa-miR-30c==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002460)
hsa-miR-30a-5p	5 8 3	V\$IRF _Q6	98	22	0.0003 887	4.092	0.2	0.00073	hsa-miR-30a-5p==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002460)
hsa-miR-30d	5 8 4	V\$IRF _Q6	98	22	0.0003 981	4.040 6	0.2	0.00073	hsa-miR-30d==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002460)
hsa-miR-23a	3 5 5	V\$IRF _Q6	98	16	0.0004 111	3.549 6	0.2	0.00073	hsa-miR-23a==> TF cluster 150:

									V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_0 1, hsa-miR- 23a==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002198 NM_002199)
hsa-miR- 144	3 9 9	V\$TG IF_01	63	13	0.0004 198	4.131	0.2	0.00073	hsa-miR- 144==> TF cluster 291: V\$TGIF_01, (NM_003244)
hsa-miR- 30c	5 8 2	V\$ME F2_03	50	14	0.0004 231	3.789	0.2	0.00073	V\$HMEF2_Q6==>h sa-miR-30c in cluster cluster5_hsa-mir-30e
hsa-miR- 30e-5p	5 8 7	V\$IRF _Q6	98	22	0.0004 279	3.586 7	0.2	0.00073	hsa-miR-30e- 5p==> TF cluster 152: V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002460)
hsa-miR- 30e-5p	5 8 7	V\$ME F2_03	50	14	0.0004 621	3.483 3	0.2	0.00073	V\$HMEF2_Q6==>hsa-miR-30e-5p in cluster cluster5_hsa-mir-30e
hsa-miR- 183	1 9 2	V\$SO X5_01	54	8	0.0004 63	3.650 1	0.2	0.00073	V\$SOX_Q6==>hsa-miR-183 in cluster cluster242_hsa-mir-183
hsa-miR- 23b	3 5 9	V\$IRF _Q6	98	16	0.0004 659	3.961 9	0.2	0.00073	hsa-miR- 23b==> TF cluster 150: V\$IRF1_01, V\$IRF_Q6, V\$IRF_Q6_0 1, hsa-miR- 23b==> TF cluster 151: V\$IRF2_01, V\$IRF_Q6, V\$IRF_Q6_0 1, (NM_002198 NM_002199)
hsa-miR- 30a-3p	2 0 4	V\$OC T_Q6	205	18	0.0004 669	3.509 7	0.2	0.00073	V\$POU3F2_01==>h sa-miR-30a-3p in cluster cluster224_hsa-mir- 30a
hsa-miR- 30e-3p	2 0 4	V\$OC T_Q6	205	18	0.0004 669	3.572 1	0.2	0.00073	hsa-miR-30e- 3p==> TF cluster 215: V\$OCT_Q6, (NM_006237)

									(NM_006237)
hsa-miR-148a	2 9 7	V\$FO X_Q2	85	13	0.0005 022	3.941 8	0.2	0.00073	hsa-miR-148a==> TF cluster 83: V\$FOX_Q2, (NM_004514)
hsa-miR-148b	2 9 7	V\$FO X_Q2	85	13	0.0005 022	3.444	0.2	0.00073	hsa-miR-148b==> TF cluster 83: V\$FOX_Q2, (NM_004514)
hsa-miR-152	2 9 9	V\$FO X_Q2	85	13	0.0005 355	3.847 5	0.2	0.00073	hsa-miR-152==> TF cluster 83: V\$FOX_Q2, (NM_004514)
hsa-miR-30e-3p	2 0 4	V\$ME F2_04	93	11	0.0005 36	4.504 9	0.2	0.00073	V\$HMEF2_Q6==>hsa-miR-30e-3p in cluster cluster5_hsa-mir-30e
hsa-miR-129	1 8 5 1	V\$NK X61_0	103	11	0.0005 653	3.602 2	0.2	0.00073	V\$NKX61_01==>hsa-miR-129 in cluster cluster40_hsa-mir-129-2
hsa-miR-10a	1 2 3	V\$IRF 2_01	108	9	0.0005 843	3.781	0.2	0.00073	V\$IRF2_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a
hsa-miR-129	1 8 5	V\$CD P_02	138	13	0.0006 167	3.08	0.2	0.00073	V\$CDP_01==>hsa-miR-129 in cluster cluster40_hsa-mir-129-2
hsa-miR-198	2 2 8	V\$SR F_01	85	11	0.0006 297	3.800 9	0.2	0.00073	hsa-miR-198==> TF cluster 267: V\$SRF_01, V\$SRF_C, V\$SRF_Q4, V\$SRF_Q5_01, V\$SRF_Q5_02, V\$SRF_Q6, (NM_003131)
hsa-miR-10a	1 2 3	V\$IRF 7_01	110	9	0.0006 685	4.033 9	0.2	0.00073	V\$IRF7_01==>hsa-miR-10a in cluster cluster111_hsa-mir-10a
hsa-miR-136	1 1 9	V\$EV I1_06	70	7	0.0006 75	4.522 9	0.2	0.00073	V\$EVII_04==>hsa-miR-136 in cluster cluster77_hsa-mir-493
hsa-miR-32	4 1 3	V\$ET S_Q4	11	5	0.0006 988	4.513 4	0.2	0.00073	hsa-miR-32==> TF cluster 72: V\$ETS_Q4, (NM_002017)
hsa-miR-124a	5 2 4 1	V\$FO XJ2_0	71	16	0.0007 236	3.628 9	0.2	0.00073	V\$FOXJ2_02==>hsa-miR-124a in cluster cluster251_hsa-mir-124a-1

hsa-miR-302c	2 8 7	V\$NF Y_C	139	17	0.0007 255	3.474 4	0.2	0.00073		hsa-miR-302c==> TF cluster 36: V\$NFY_C, V\$NFY_Q6, V\$NFY_Q6_01, (NM_002505)
hsa-miR-302a	3 1 6	V\$NF Y_C	139	18	0.0007 983	3.547 6	0.3	0.00218		hsa-miR-302a==> TF cluster 36: V\$NFY_C, V\$NFY_Q6, V\$NFY_Q6_01, (NM_002505)
hsa-miR-93	4 9 5	V\$E2 F_Q3_01	6	4	0.0008 034	6.547 9	0.3	0.00218	V\$E2F_01,V\$E2F_03==>hsa-miR-93 in cluster cluster238_hsa-mir-106b	hsa-miR-93==> TF cluster 58: V\$E2F1_Q3_01, V\$E2F1_Q4_01, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02, V\$E2F_03, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-93==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949 NM_005225)
hsa-let-7f	4 4 8	V\$ET S1_B	53	12	0.0008 101	3.952 9	0.3	0.00218		hsa-let-7f==> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-101	3 9	V\$FO X_Q2	85	15	0.0008 551	3.354 3	0.3	0.00218	V\$FOXO4_02,V\$FREAC2_01==>hsa-miR-101 in cluster cluster6_hsa-	

	7								mir-101-1	
hsa-miR-144	3 9 9	V\$FOX_Q2	85	15	0.0009 007	3.327 5	0.3	0.00218		hsa-miR-144==> TF cluster 96: V\$FOXO1_02, V\$FOX_Q2, (NM_002015)
hsa-miR-372	5 1 1	V\$E2F_Q3_01	6	4	0.0009 082	6.473 5	0.3	0.00218		hsa-miR-372==> TF cluster 58: V\$E2F1_Q3_01, V\$E2F1_Q4, V\$E2F1_Q4_01, V\$E2F1_Q6, V\$E2F1_Q6_01, V\$E2F_01, V\$E2F_02, V\$E2F_03, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, hsa-miR-372==> TF cluster 62: V\$E2F1_Q4_01, V\$E2F_02, V\$E2F_Q3_01, V\$E2F_Q4_01, V\$E2F_Q6_01, (NM_001949 NM_005225)
hsa-miR-92	3 8 3	V\$FOXJ2_01	71	13	0.0009 436	3.744 1	0.3	0.00218	V\$FOXJ2_02==>hsa-miR-92 in cluster cluster292_hsa-mir-106a	
hsa-miR-132	1 7 6	V\$AP1_Q4	25	5	0.0009 506	4.751 6	0.3	0.00218	V\$AP1_01,V\$AP1_Q4==>hsa-miR-132 in cluster cluster101_hsa-mir-212	TFs unmapped
hsa-miR-212	1 7 6	V\$AP1_Q4	25	5	0.0009 506	4.463 8	0.3	0.00218	V\$AP1_01,V\$AP1_Q4==>hsa-miR-212 in cluster cluster101_hsa-mir-212	TFs unmapped
hsa-miR-181a	4 4 2	V\$ETS_Q4	11	5	0.0009 559	4.349 9	0.3	0.00218		hsa-miR-181a==> TF cluster 72: V\$ETS_Q4, hsa-miR-181a==> TF

										cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-181b	4 4 2	V\$ET S_Q4	11	5	0.0009 559	4.285 1	0.3	0.00218		hsa-miR-181b==> TF cluster 72: V\$ETS_Q4, hsa-miR-181b==> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-181c	4 4 2	V\$ET S_Q4	11	5	0.0009 559	4.568 5	0.3	0.00218		hsa-miR-181c==> TF cluster 72: V\$ETS_Q4, hsa-miR-181c==> TF cluster 308: V\$ETS1_B, V\$ETS_Q4, (NM_005238)
hsa-miR-22	2 3 9	V\$M MEF2 Q6	99	12	0.0009 983	3.278 4	0.3	0.00218	V\$AMEF2_Q6==>hsa-miR-22 in cluster cluster100_hsa-mir-22	
hsa-miR-93	4 9 5	V\$PP ARA_ 02	43	11	0.0010 236	3.894 3	0.3	0.00218	V\$DR4_Q2,V\$PPA RA_02==>hsa-miR- 93 in cluster cluster238_hsa-mir- 106b	hsa-miR-93==> TF cluster 229: V\$PPARA_01 , V\$PPARA_02 , V\$PPAR_DR 1_Q2, (NM_005036)
hsa-miR-372	5 1 1	V\$HN F3_Q6 _01	42	11	0.0010 788	3.939 2	0.3	0.00218		hsa-miR-372==> TF cluster 127: V\$HNF3ALP HA_Q6, V\$HNF3_Q6, V\$HNF3_Q6_ 01, (NM_004496)
hsa-miR-137	3 2 6	V\$EV I1_03	74	12	0.0010 921	3.892 6	0.3	0.00218	V\$EV11_04==>hsa- miR-137 in cluster cluster8_hsa-mir-137	TFs unmapped
hsa-miR-142-3p	1 4 2	V\$YY 1_02	123	10	0.0010 95	3.793 7	0.3	0.00218	V\$YY1_02==>hsa-miR-142-3p in cluster cluster113_hsa-mir-142	
hsa-miR-137	3 2 6	V\$CIZ _01	37	8	0.0011 02	3.924 7	0.3	0.00218	V\$CIZ_01==>hsa- miR-137 in cluster cluster8_hsa-mir-137	TFs unmapped

hsa-miR-34b	2 2 9	V\$EV I1_01	77	10	0.0011 138	4.495 6	0.3	0.00218	V\$EVI1_03==>hsa-miR-34b in cluster cluster47_hsa-mir-34b	TFs unmapped
hsa-miR-129	1 8 5	V\$SP3 _Q3	64	8	0.0011 545	3.470 9	0.3	0.00218		hsa-miR-129==> TF cluster 282: V\$SP3_Q3, (NM_003111)
hsa-miR-96	5 0 0 2	V\$CR EB_Q	85	17	0.0012 262	3.073 3	0.3	0.00218	V\$CREB_Q2_01==>hsa-miR-96 in cluster cluster242_hsa-mir-183	hsa-miR-96==> TF cluster 46: V\$CREBATF_Q6, V\$CREB_01, V\$CREB_02, V\$CREB_Q2_01, V\$CREB_Q4_01, V\$TAXCREB_01, V\$TAXCREB_02, (NM_004379)
hsa-miR-144	3 9 9	V\$NR F2_Q4	106	17	0.0012 867	3.521	0.3	0.00218		hsa-miR-144==> TF cluster 214: V\$MAF_Q6_01, V\$NRF2_Q4, (NM_006164)
hsa-miR-20a	5 2 4	V\$HN F3_Q6_01	42	11	0.0013 283	4.298 7	0.3	0.00218		hsa-miR-20a==> TF cluster 127: V\$HNF3ALP_HA_Q6, V\$HNF3_Q6_01, (NM_004496)
hsa-miR-106b	5 2 7	V\$HN F3_Q6_01	42	11	0.0013 923	4.238 9	0.3	0.00218		hsa-miR-106b==> TF cluster 127: V\$HNF3ALP_HA_Q6, V\$HNF3_Q6_01, (NM_004496)
hsa-miR-194	1 8 0	V\$HN F3AL PHA	53	7	0.0014 463	3.426 9	0.3	0.00218		hsa-miR-194==> TF cluster 127:

		Q6							V\$HNF3ALP HA_Q6, V\$HNF3_Q6, V\$HNF3_Q6_01, (NM_004496)
hsa-miR-302c	287	V\$SP3_Q3	64	10	0.0014483	3.2214	0.3	0.00218	hsa-miR-302c=> TF cluster 282: V\$SP3_Q3, (NM_003111)
hsa-miR-196a	123	V\$MMEF2_Q6	99	8	0.0014483	3.7379	0.3	0.00218	V\$MEF2_Q3=>hsa-miR-196a in cluster cluster53_hsa-mir-196a-2
hsa-miR-22	2391	V\$CMYB_0	52	8	0.0015069	3.3864	0.3	0.00218	V\$MYB_Q3=>hsa-miR-22 in cluster cluster100_hsa-mir-22
hsa-miR-30a-5p	5831	V\$HNF3B_0	75	17	0.0015575	3.3262	0.3	0.00218	V\$HNF3B_Q6=>hsa-miR-30a-5p in cluster cluster224_hsa-mir-30a
hsa-miR-218	384	V\$PR_Q1	49	10	0.0015722	3.5091	0.3	0.00218	V\$PR_Q2=>hsa-miR-218 in cluster cluster216_hsa-mir-218-2
hsa-miR-1	373	V\$OCT1_T1_03	27	7	0.0015814	4.5194	0.3	0.00218	V\$OCT1_B=>hsa-miR-1 in cluster cluster122_hsa-mir-1-2
hsa-miR-199a-star	3932	V\$FOXJ2_0	179	24	0.0016087	2.6908	0.3	0.00218	V\$FOXJ2_Q1,V\$FOX_Q2=>hsa-miR-199a-star in cluster cluster17_hsa-mir-199a-2
hsa-miR-1	373	V\$EVII_01	77	13	0.0016132	3.9081	0.3	0.00218	V\$EVII_Q3,V\$EVII_Q4=>hsa-miR-1 in cluster cluster122_hsa-mir-1-2
hsa-miR-122a	110	V\$DEC_Q1	44	5	0.0016215	4.3785	0.3	0.00218	hsa-miR-122a=> TF cluster 23: V\$DEC_Q1, (NM_030762)
hsa-miR-142-5p	261	V\$SRF_Q6	85	11	0.0019058	3.0794	0.3	0.00218	hsa-miR-142-5p=> TF cluster 267: V\$SRF_Q1, V\$SRF_Q4, V\$SRF_Q5_01, V\$SRF_Q5_02, V\$SRF_Q6, (NM_003131)
hsa-miR-92	38	V\$RFX_Q6	51	10	0.0021184	3.5727	0.3	0.00218	V\$RFX_Q1=>hsa-miR-92 in cluster

	3							cluster12_hsa-mir-92b	cluster 251: V\$EFC_Q6, V\$RFX1_Q1, V\$RFX1_Q2, V\$RFX_Q6, (NM_002918)
hsa-miR-128b	4 V\$FO 7 XO3_ 4 01	94	17	0.0021 578	3.175 5	0.3	0.00218	V\$FOX_Q2==>hsa-miR-128b in cluster cluster176_hsa-mir-128b	

Table 11 - miR-TF FFLs in the PicTar network, 5kb promoters.

All the pairs in this table passed FDR of 0.3 or less in the hyper-geometric p-value for co-occurrence, and also received a co-occurrence p-value <10E-3 in the randomization-based test. if a pair also constitutes an FFL, the following data is provided in the last columns: TF==> miR: we provide the PSSMS and the genomic miR cluster for which a binding site was found for the PSSMs indicated. if more than one connection exists, all are specified. miR==>TF: we indicate which miR (out of the clusters from which the partner miR is transcribed) was found to have a binding site, and the RefSeq ID of the partner PSSM, in which the miR site is found. "TF unmapped" indicates that the PSSM could not be mapped to a SwissProt ID using the UCSC hg17 tfbsConsFactors track.

In the next step, the present inventors looked for another type of network motif, that was termed an "indirect FFL", in which the TF's regulation on its partner miR is exerted via another mediator TF. The present inventors looked to see if any of the miR-TF partners in the network had a conserved TF binding site in a promoter of at least one other TF, which in turn has a conserved binding site in the promoter of the partner miR. Significantly, this architecture was very common in the present networks; 30 of the TF-miR partners in the TargetScan network (28 %) and 201 partners in the PicTar network (22 %) were connected in a regulatory path between the TF and the miR via another TF. The significance of these results was tested by a randomization test, similar to that described above (see Materials and Methods), and received a p -value of 1.3×10^{-3} for the appearance of the indirect FFL in the TargetScan network, and p -value $< 10^{-4}$ for the PicTar network (see Figure 4).

Table 12 herein below lists pairs of indirect FFLs in the TargetScan database.

Table 12

<i>miR</i>	<i>TF</i>	<i>has a regular FFL</i>	<i>indirect FFL information</i>
miR-28	V\$AHR_Q5	NO	diamond to cluster191_hsa-mir-28 via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
miR-324-5p	V\$AIRE_02	NO	diamond to cluster103_hsa-mir-324 via NM_006626 (V\$ZID_01)
miR-503	V\$CDPCR1_01	TF2mir	diamond to cluster293_hsa-mir-424 via NM_002398(V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02 V\$MEIS1_01) NM_012448 (V\$STAT5B_01 V\$STAT_01 V\$STAT_Q6)
miR-505	V\$CDPCR1_01	NO	diamond to cluster295_hsa-mir-505 via NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02 V\$MEIS1_01)
miR-93	V\$CDPCR1_01	NO	diamond to cluster238_hsa-mir-106b via NM_005654(V\$COUP_01 V\$COUP_ DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
miR-7	V\$CDP_02	TF2mir	diamond to cluster92_hsa-mir-7-2 via NM_001674(V\$ATF3_Q6 V\$CREBATF_Q6)
miR-15	V\$CDX2_Q5	NO	diamond to cluster188_hsa-mir-15b via NM_000306 (V\$PIT1_Q6 V\$POU1F1_Q6)
miR-93	V\$E2F_Q3_01	TF2mir	diamond to cluster238_hsa-mir-106b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
miR-135	V\$E2F_Q4	NO	diamond to cluster20_hsa-mir-135b via NM_005585 (V\$SMAD_Q6_01)
miR-28	V\$FOXO4_02	NO	diamond to cluster191_hsa-mir-28 via NM_002229 (V\$API_01 V\$API_Q2_01)
miR-129	V\$GFI1_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_001880 (V\$CREBATF_Q6 V\$CREBP1CJUN_01 V\$CREBP1_01 V\$CREBP1_Q2)NM_004599 (V\$SREBP_Q3)NM_004852 (V\$HNF6_Q6)NM_005920 (V\$MEF2_Q6_01)
miR-30	V\$HIF1_Q5	NO	diamond to cluster224_hsa-mir-30a via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
miR-375	V\$HMGIIY_Q3	NO	diamond to cluster149_hsa-mir-375 via NM_004498 (V\$HNF6_Q6)
miR-505	V\$HNF6_Q6	TF2mir	diamond to cluster295_hsa-mir-505 via NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02 V\$MEIS1_01) NM_004498 (V\$HNF6_Q6) NM_004852 (V\$HNF6_Q6)
miR-19	V\$IRF_Q6	NO	diamond to cluster70_hsa-mir-17 via NM_000438 (V\$PAX3_01 V\$PAX3_ B V\$PAX_Q6)NM_007129 (V\$ZIC2_01)
miR-30	V\$IRF_Q6	mir2TF	diamond to cluster223_hsa-mir-30c-2 via NM_000325(V\$PTX2_Q2)
miR-33	V\$NKX25_01	NO	diamond to cluster104_hsa-mir-33b via NM_005654 (V\$COUP_01 V\$COUP_

			DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
miR-23	V\$NKX25_02	NO	diamond to cluster129_hsa-mir-23a via NM_003204(V\$MAF_Q6_01 V\$TCF11MAFG_01 V\$TCF11_01)
miR-135	V\$NRSF_01	NO	diamond to cluster64_hsa-mir-135a-2 via NM_014564 (V\$LHX3_01)
miR-153	V\$NRSF_01	NO	diamond to cluster150_hsa-mir-153-1 via NM_003403 (V\$YY1_01 V\$YY1_02 V\$YY1_Q6)NM_014587 (V\$SOX_Q6)
miR-26	V\$POU3F2_02	NO	diamond to cluster177_hsa-mir-26a-1 via NM_002955 (V\$RREB1_01) NM_004852 (V\$HNF6_Q6)
miR-10	V\$POU6F1_01	TF2mir	diamond to cluster111_hsa-mir-10a via NM_003106 (V\$SOX_Q6)
miR-186	V\$POU6F1_01	NO	diamond to cluster7_hsa-mir-186 via NM_002142 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02)
miR-218	V\$POU6F1_01	NO	diamond to cluster196_hsa-mir-218-1 via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
miR-33	V\$S8_01	NO	diamond to cluster104_hsa-mir-33b via NM_005654 (V\$COUP_01 V\$COUP_DR1_ Q6 V\$DR1_Q3 V\$DR4_Q2)
miR-22	V\$SRF_Q4	mir2TF	diamond to cluster100_hsa-mir-22 via NM_001964 (V\$EGR1_01 V\$EGR_Q6 V\$KROX_Q6)
miR-19	V\$SRF_Q6	NO	diamond to cluster292_hsa-mir-106a via NM_001965 (V\$KROX_ Q6 V\$NGFIC_01)
miR-141	V\$TATA_01	NO	diamond to cluster50_hsa-mir-200c via NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_ Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)
miR-194	V\$TST1_01	NO	diamond to cluster43_hsa-mir-194-2 via NM_000278 (V\$PAX2_01 V\$PAX_Q6)
miR-210	V\$ZF5_B	NO	diamond to cluster37_hsa-mir-210 via NM_006237(V\$OCT_Q6)

Table 13 herein below lists pairs of indirect FFLs in the PicTar database taking 10kb regulatory regions for protein coding genes.

Table 13

miR	TF	has a regular FFL	indirect FFL information
hsa-miR-24	V\$AFP1_Q6	NO	diamond to cluster129_hsa-mir-23a via NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)NM_004176 (V\$SREBP1_01 V\$SREBP1_02 V\$SREBP_Q3)
hsa-miR-10a	V\$AIRE_02	TF2mir	diamond to cluster111_hsa-mir-10a via NM_003106 (V\$SOX_Q6)NM_003108 (V\$SOX_Q6)
hsa-miR-28	V\$AP1_Q2_01	TF2mir	diamond to cluster191_hsa-mir-28 via NM_002229 (V\$AP1_01 V\$AP1_Q2_01)
hsa-	V\$AP1_Q4	TF2mir	diamond to cluster101_hsa-mir-212 via NM_001186 (

miR-132			V\$BACH1_01 V\$MAF_Q6_01)
hsa-miR-212	V\$AP1_Q4	TF2mir	diamond to cluster101_hsa-mir-212 via NM_001186 (V\$BACH1_01 V\$MAF_Q6_01)
hsa-miR-214	V\$ARNT_Q2	NO	diamond to cluster17_hsa-mir-199a-2 via NM_012183 (V\$FOXD3_01 V\$FOX_Q2)NM_021953 (V\$FOX_Q2)
hsa-miR-10a	V\$ATF1_Q6	NO	diamond to cluster111_hsa-mir-10a via NM_002918 (V\$EFC_Q6 V\$RFX1_01 V\$RFX1_Q2 V\$RFX_Q6)
hsa-miR-182	V\$ATF1_Q6	NO	diamond to cluster242_hsa-mir-183 via NM_002918 (V\$EFC_Q6 V\$RFX1_01 V\$RFX1_Q2 V\$RFX_Q6)
hsa-miR-19a	V\$ATF4_Q2	NO	diamond to cluster70_hsa-mir-17 via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-19b	V\$ATF4_Q2	NO	diamond to cluster70_hsa-mir-17 via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-206	V\$ATF_B	NO	diamond to cluster222_hsa-mir-206 via NM_005920 (V\$MEF2_Q6_01)
hsa-miR-302c-star	V\$CART1_01	NO	diamond to cluster201_hsa-mir-302b via NM_002697 (V\$OCT1_01 V\$OCT1_Q2 V\$OCT1_Q3 V\$OCT1_Q4 V\$OCT1_Q5 V\$OCT1_Q6 V\$OCT1_Q7 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-324-5p	V\$CART1_01	NO	diamond to cluster103_hsa-mir-324 via NM_002015 (V\$FOXO1_Q2 V\$FOX_Q2)NM_006626 (V\$ZID_01)
hsa-miR-153	V\$CDPCR1_01	NO	diamond to cluster247_hsa-mir-153-2 via NM_012183 (V\$FOXD3_01 V\$FOX_Q2)
hsa-miR-15b	V\$CDPCR1_01	TF2mir	diamond to cluster188_hsa-mir-15b via NM_012448 (V\$STAT5B_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-16	V\$CDPCR1_01	TF2mir	diamond to cluster188_hsa-mir-15b via NM_012448 (V\$STAT5B_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-186	V\$CDPCR1_01	NO	diamond to cluster7_hsa-mir-186 via NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_Q2 V\$MEIS1_01)
hsa-miR-195	V\$CDPCR1_01	NO	diamond to cluster102_hsa-mir-497 via NM_002052 (V\$GATA4_Q3)
hsa-miR-199a	V\$CDPCR1_01	NO	diamond to cluster17_hsa-mir-199a-2 via NM_012183 (V\$FOXD3_01 V\$FOX_Q2)NM_018416 (V\$FOXJ2_01 V\$FOXJ2_Q2 V\$FOX_Q2)
hsa-miR-199b	V\$CDPCR1_01	NO	diamond to cluster275_hsa-mir-199b via NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_Q2 V\$MEIS1_01)NM_012448 (V\$STAT5B_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-217	V\$CDPCR1_01	TF2mir	diamond to cluster143_hsa-mir-216 via NM_002051 (V\$GATA3_01 V\$GATA_C)
hsa-miR-29b	V\$CDPCR1_01	NO	diamond to cluster21_hsa-mir-29b-2 via NM_002052 (V\$GATA4_Q3)NM_012183 (V\$FOXD3_01 V\$FOX_Q2)NM_018416 (V\$FOXJ2_01

			V\$FOXJ2_02 V\$FOX_Q2)
hsa-miR-29c	V\$CDPCR1_01	NO	diamond to cluster21_hsa-mir-29b-2 via NM_002052 (V\$GATA4_Q3)NM_012183 (V\$FOX_D3_01 V\$FOX_Q2)NM_018416 (V\$FOXJ2_01 V\$FOXJ2_02 V\$FOX_Q2)
hsa-miR-320	V\$CDPCR1_01	NO	diamond to cluster254_hsa-mir-320 via NM_018416 (V\$FOXJ2_01 V\$FOXJ2_02 V\$FOX_Q2)
hsa-miR-122a	V\$CDP_01	NO	diamond to cluster124_hsa-mir-122a via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-181c	V\$CDP_01	TF2mir	diamond to cluster130_hsa-mir-181c via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-196b	V\$CDP_01	NO	diamond to cluster232_hsa-mir-196b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-30a-5p	V\$CDP_01	NO	diamond to cluster224_hsa-mir-30a via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)NM_012183 (V\$FOX_D3_01 V\$FOX_Q2)
hsa-miR-18b	V\$CDP_02	NO	diamond to cluster292_hsa-mir-106a via NM_000278 (V\$PAX2_01 V\$PAX_Q6)
hsa-miR-130a	V\$CDX2_Q5	NO	diamond to cluster41_hsa-mir-130a via NM_003403 (V\$YY1_01 V\$YY1_02 V\$YY1_Q6)
hsa-miR-15b	V\$CDX2_Q5	NO	diamond to cluster188_hsa-mir-15b via NM_000306 (V\$PIT1_Q6 V\$POU1F1_Q6)
hsa-miR-16	V\$CDX2_Q5	NO	diamond to cluster188_hsa-mir-15b via NM_000306 (V\$PIT1_Q6 V\$POU1F1_Q6)
hsa-miR-183	V\$CEBP_C	NO	diamond to cluster242_hsa-mir-183 via NM_003106 (V\$SOX_Q6)
hsa-miR-9-star	V\$CHX10_01	NO	diamond to cluster14_hsa-mir-9-1 via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-182	V\$COMP1_01	NO	diamond to cluster242_hsa-mir-183 via NM_018419 (V\$SOX_Q6)
hsa-miR-125b	V\$CREBATF_Q6	NO	diamond to cluster165_hsa-mir-125b-2 via NM_003150 (V\$STAT3_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-93	V\$CREB_Q2	NO	diamond to cluster238_hsa-mir-106b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)NM_021976 (V\$DR3_Q4 V\$DR4_Q2)
hsa-miR-186	V\$CREB_Q4	NO	diamond to cluster7_hsa-mir-186 via NM_001489 (V\$GCNF_01)
hsa-miR-10b	V\$DR4_Q2	NO	diamond to cluster146_hsa-mir-10b via NM_003216 (V\$TEF_Q6)
hsa-miR-210	V\$E2F_01	NO	diamond to cluster37_hsa-mir-210 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)

hsa-miR-183	V\$E2F_Q3	NO	diamond to cluster242_hsa-mir-183 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)NM_004189 (V\$SOX_Q6)
hsa-miR-93	V\$E2F_Q3_01	TF2mir mir2TF	diamond to cluster238_hsa-mir-106b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-135b	V\$E2F_Q4	NO	diamond to cluster20_hsa-mir-135b via NM_005585 (V\$SMAD_Q6_01)
hsa-miR-129	V\$E4BP4_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_006195 (V\$PBX_Q3)
hsa-miR-19b	V\$E4BP4_01	NO	diamond to cluster292_hsa-mir-106a via NM_001964 (V\$EGR1_01 V\$EGR_Q6 V\$KROX_Q6)
hsa-miR-7	V\$ETS_Q4	NO	diamond to cluster267_hsa-mir-7-1 via NM_001265 (V\$CDX_Q5)
hsa-miR-10b	V\$FAC1_01	NO	diamond to cluster146_hsa-mir-10b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-101	V\$FOXJ2_01	NO	diamond to cluster263_hsa-mir-101-2 via NM_000457 (V\$COUP_01 V\$DR1_Q3 V\$HNF4ALPHA_Q6 V\$HNF4_01 V\$HNF4_01_B V\$HNF4_DR1_Q3)NM_004364 (V\$CEBPA_01 V\$CEBP_01 V\$CEBP_C V\$CEBP_Q2 V\$CEBP_Q2_01 V\$CEBP_Q3 V\$CHOP_01)
hsa-miR-130a	V\$FOXJ2_01	NO	diamond to cluster41_hsa-mir-130a via NM_004364 (V\$CEBPA_01 V\$CEBP_01 V\$CEBP_C V\$CEBP_Q2 V\$CEBP_Q2_01 V\$CEBP_Q3 V\$CHOP_01)
hsa-miR-23a	V\$FOXJ2_01	NO	diamond to cluster129_hsa-mir-23a via NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02 V\$MEIS1_01)NM_004364 (V\$CEBPA_01 V\$CEBP_01 V\$CEBP_C V\$CEBP_Q2 V\$CEBP_Q2_01 V\$CEBP_Q3 V\$CHOP_01)
hsa-miR-25	V\$FOXJ2_01	NO	diamond to cluster238_hsa-mir-106b via NM_000964 (V\$DR4_Q2)NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-342	V\$FOXJ2_01	NO	diamond to cluster75_hsa-mir-342 via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-129	V\$FOXJ2_02	TF2mir	diamond to cluster40_hsa-mir-129-2 via NM_004176 (V\$SREBP1_01 V\$SREBP1_02 V\$SREBP_Q3)NM_005587 (V\$AMEF2_Q6 V\$HMEF2_Q6 V\$MEF2_01 V\$MEF2_02 V\$MEF2_03 V\$MEF2_04 V\$MEF2_Q6_01 V\$MMEF2_Q6)
hsa-miR-33	V\$FOXJ2_02	NO	diamond to cluster104_hsa-mir-33b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-129	V\$FOXMI_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_006195 (V\$PBX_Q3)
hsa-miR-92	V\$FOXO4_01	NO	diamond to cluster292_hsa-mir-106a via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)NM_004852 (V\$HNF6_Q6)
hsa-miR-101	V\$FOXP1_01	NO	diamond to cluster6_hsa-mir-101-1 via NM_001453 (V\$FREAC3_01)
hsa-miR-	V\$FOXP1_01	NO	diamond to cluster274_hsa-mir-181a via NM_002015 (V\$FOXO1_02 V\$FOX_Q2)

181a			
hsa-miR-181b	V\$FOXP1_01	NO	diamond to cluster274_hsa-mir-181a via NM_002015 (V\$FOXO1_02 V\$FOX_Q2)
hsa-miR-194	V\$FOXP1_01	NO	diamond to cluster43_hsa-mir-194-2 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-196b	V\$FOXP1_01	NO	diamond to cluster232_hsa-mir-196b via NM_001453 (V\$FREAC3_01)NM_004472 (V\$FREAC4_01)
hsa-miR-199a-star	V\$FOXP1_01	NO	diamond to cluster17_hsa-mir-199a-2 via NM_002015 (V\$FOXO1_02 V\$FOX_Q2)
hsa-miR-9-star	V\$FOXP1_01	TF2mir	diamond to cluster93_hsa-mir-9-3 via NM_006352 (V\$RP58_01)
hsa-miR-92	V\$FOXP1_01	TF2mir	diamond to cluster292_hsa-mir-106a via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)NM_004348 (V\$AML_Q6 V\$PEBP_Q6)NM_004498 (V\$HNF6_Q6)NM_005036 (V\$PPARA_01 V\$PPARA_Q2 V\$PPAR_DR1_Q2)
hsa-miR-28	V\$FREAC2_01	NO	diamond to cluster191_hsa-mir-28 via NM_005253 (V\$AP1_Q2_01)
hsa-miR-129	V\$FREAC3_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_004852 (V\$HNF6_Q6)NM_006195 (V\$PBX_Q3)
hsa-miR-194	V\$FREAC3_01	NO	diamond to cluster43_hsa-mir-194-2 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)NM_006164 (V\$MAF_Q6_01 V\$NRF2_Q4)
hsa-miR-28	V\$FREAC4_01	NO	diamond to cluster191_hsa-mir-28 via NM_002229 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-199b	V\$FREAC7_01	NO	diamond to cluster275_hsa-mir-199b via NM_001621 (V\$AHRARNT_01 V\$AHRARNT_Q2 V\$AHR_Q1 V\$AHR_Q5)NM_002142 (V\$MEIS1AHXA9_01 V\$MEIS1BHXA9_Q2)
hsa-miR-96	V\$FREAC7_01	NO	diamond to cluster242_hsa-mir-183 via NM_001621 (V\$AHRARNT_01 V\$AHRARNT_Q2 V\$AHR_Q1 V\$AHR_Q5)
hsa-miR-10a	V\$GATA1_05	NO	diamond to cluster111_hsa-mir-10a via NM_000325 (V\$PITX2_Q2)NM_003108 (V\$SOX_Q6)
hsa-miR-10b	V\$GATA1_05	NO	diamond to cluster146_hsa-mir-10b via NM_002052 (V\$GATA4_Q3)
hsa-miR-20b	V\$GATA1_05	NO	diamond to cluster292_hsa-mir-106a via NM_002699 (V\$OCT_Q6 V\$TST1_01)
hsa-miR-182	V\$HIF1_Q3	NO	diamond to cluster242_hsa-mir-183 via NM_003108 (V\$SOX_Q6)
hsa-miR-182	V\$HIF1_Q5	NO	diamond to cluster242_hsa-mir-183 via NM_003106 (V\$SOX_Q6)
hsa-miR-30a-5p	V\$HIF1_Q5	NO	diamond to cluster224_hsa-mir-30a via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-	V\$HMG1Y_Q3	NO	diamond to cluster242_hsa-mir-183 via NM_006942 (V\$SOX_Q6)

183			
hsa-miR-375	V\$HMG1Y_Q3	NO	diamond to cluster149_hsa-mir-375 via NM_004498 (V\$HNF6_Q6)
hsa-miR-331	V\$HNF1_C	NO	diamond to cluster63_hsa-mir-331 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-182	V\$HNF3ALPHA_Q6	NO	diamond to cluster242_hsa-mir-183 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-9-star	V\$HNF3ALPHA_Q6	NO	diamond to cluster209_hsa-mir-9-2 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-96	V\$HNF3ALPHA_Q6	NO	diamond to cluster242_hsa-mir-183 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-137	V\$HNF3B_01	NO	diamond to cluster8_hsa-mir-137 via NM_002509 (V\$NKX22_01)NM_014564 (V\$LHX3_01)
hsa-miR-199b	V\$HNF3B_01	NO	diamond to cluster275_hsa-mir-199b via NM_007348 (V\$ATF6_01 V\$CREBATF_Q6)
hsa-miR-153	V\$HNF6_Q6	TF2mir	diamond to cluster150_hsa-mir-153-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)NM_003107 (V\$SOX_Q6)NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)NM_006940 (V\$SOX5_01 V\$SOX_Q6)
hsa-miR-367	V\$HNF6_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-146b	V\$ICSBP_Q6	NO	diamond to cluster34_hsa-mir-146b via NM_003153 (V\$STAT_01 V\$STAT_Q6)NM_005419 (V\$STAT_01 V\$STAT_Q6)
hsa-miR-103	V\$IRF1_01	NO	diamond to cluster215_hsa-mir-103-1 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-10a	V\$IRF7_01	TF2mir	diamond to cluster111_hsa-mir-10a via NM_002199 (V\$IRF2_01 V\$IRF_Q6 V\$IRF_Q6_01)
hsa-miR-10b	V\$IRF7_01	NO	diamond to cluster146_hsa-mir-10b via NM_003998 (V\$NFKAPPAB50_01 V\$NFKAPPAB_01 V\$NFKB_C V\$NFKB_Q6 V\$NFKB_Q6_01)
hsa-miR-9-star	V\$IRF7_01	NO	diamond to cluster209_hsa-mir-9-2 via NM_004852 (V\$HNF6_Q6)
hsa-miR-135a	V\$IRF_Q6	NO	diamond to cluster64_hsa-mir-135a-2 via NM_004852 (V\$HNF6_Q6)NM_014009 (V\$FOXP3_Q4)
hsa-miR-135b	V\$IRF_Q6	NO	diamond to cluster20_hsa-mir-135b via NM_000325 (V\$PITX2_Q2)
hsa-miR-19b	V\$IRF_Q6	NO	diamond to cluster70_hsa-mir-17 via NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)NM_007129 (V\$ZIC2_01)
hsa-miR-	V\$IRF_Q6	NO	diamond to cluster23_hsa-mir-194-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)

215			
hsa-miR-23a	V\$IRF_Q6	mir2TF	diamond to cluster129_hsa-mir-23a via NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)
hsa-miR-23b	V\$IRF_Q6	mir2TF	diamond to cluster269_hsa-mir-23b via NM_001913 (V\$CDPCR1_01 V\$CDPCR3HD_01 V\$CDPCR3_01 V\$CDP_01 V\$CDP_02)
hsa-miR-30a-5p	V\$IRF_Q6	mir2TF	diamond to cluster224_hsa-mir-30a via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-30c	V\$IRF_Q6	mir2TF	diamond to cluster223_hsa-mir-30c-2 via NM_000325 (V\$PITX2_Q2)
hsa-miR-93	V\$IRF_Q6	mir2TF	diamond to cluster238_hsa-mir-106b via NM_002957 (V\$DR3_Q4 V\$DR4_Q2 V\$PPARA_02)NM_005654 (V\$COUP_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-219	V\$ISRE_01	NO	diamond to cluster220_hsa-mir-219-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)NM_002955 (V\$RREB1_01)
hsa-miR-302a	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-302b	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-302c	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-302d	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-191	V\$LHX3_01	NO	diamond to cluster181_hsa-mir-191 via NM_004852 (V\$HNF6_Q6)
hsa-miR-210	V\$LHX3_01	NO	diamond to cluster37_hsa-mir-210 via NM_006237 (V\$OCT_Q6)
hsa-miR-7	V\$MEF2_01	TF2mir	diamond to cluster126_hsa-mir-7-3 via NM_013435 (V\$CRX_Q4)
hsa-miR-204	V\$MEF2_04	TF2mir	diamond to cluster266_hsa-mir-204 via NM_006982 (V\$CART1_01)
hsa-miR-30a-3p	V\$MEF2_04	NO	diamond to cluster224_hsa-mir-30a via NM_021784 (V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-33	V\$MEF2_04	NO	diamond to cluster104_hsa-mir-33b via NM_005654 (V\$COUP_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-196a	V\$MMEF2_Q6	TF2mir	diamond to cluster53_hsa-mir-196a-2 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)NM_006352 (V\$RP58_01)NM_014009 (V\$FOXP3_Q4)
hsa-miR-135b	V\$MYOD_Q6_01	NO	diamond to cluster20_hsa-mir-135b via NM_000376 (V\$DR3_Q4 V\$VDR_Q3 V\$VDR_Q6)

hsa-miR-124a	V\$NFKAPPAB65_01	NO	diamond to cluster162_hsa-mir-124a-3 via NM_004379 (V\$CREBATF_Q6 V\$CREB_01 V\$CREB_02 V\$CREB_Q2 V\$CREB_Q2_01 V\$CREB_Q4 V\$CREB_Q4_01 V\$TAXCREB_01 V\$TAXCREB_02)
hsa-miR-22	V\$NFKAPPAB65_01	NO	diamond to cluster100_hsa-mir-22 via NM_007315 (V\$STAT1_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-96	V\$NFKB_Q6	NO	diamond to cluster242_hsa-mir-183 via NM_004379 (V\$CREBATF_Q6 V\$CREB_01 V\$CREB_02 V\$CREB_Q2 V\$CREB_Q2_01 V\$CREB_Q4 V\$CREB_Q4_01 V\$TAXCREB_01 V\$TAXCREB_02)NM_018419 (V\$SOX_Q6)
hsa-miR-23a	V\$NKX25_02	NO	diamond to cluster129_hsa-mir-23a via NM_003204 (V\$MAF_Q6_01 V\$TCF11MAFG_01 V\$TCF11_01)
hsa-miR-129	V\$NKX62_Q2	NO	diamond to cluster40_hsa-mir-129-2 via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-183	V\$NKX62_Q2	NO	diamond to cluster242_hsa-mir-183 via NM_003106 (V\$SOX_Q6)NM_003107 (V\$SOX_Q6)
hsa-miR-208	V\$NKX62_Q2	NO	diamond to cluster72_hsa-mir-208 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-219	V\$NKX62_Q2	NO	diamond to cluster220_hsa-mir-219-1 via NM_002955 (V\$RREB1_01)
hsa-miR-101	V\$NRF2_Q4	mir2TF	diamond to cluster263_hsa-mir-101-2 via NM_015859 (V\$TFIIA_Q6)
hsa-miR-135a	V\$NRSF_01	NO	diamond to cluster64_hsa-mir-135a-2 via NM_014564 (V\$LHX3_01)
hsa-miR-153	V\$NRSF_01	NO	diamond to cluster150_hsa-mir-153-1 via NM_003403 (V\$YY1_01 V\$YY1_02 V\$YY1_Q6)NM_014587 (V\$SOX_Q6)
hsa-miR-219	V\$OCT1_02	NO	diamond to cluster220_hsa-mir-219-1 via NM_000278 (V\$PAX2_01 V\$PAX_Q6)
hsa-	V\$OCT1_03	TF2mir	diamond to cluster102_hsa-mir-497 via NM_006856 (

miR-195			V\$CREBATF_Q6)
hsa-miR-21	V\$OCT1_05	NO	diamond to cluster115_hsa-mir-21 via NM_002460 (V\$IRF_Q6 V\$IRF_Q6_01)NM_006168 (V\$NKX61_01)
hsa-miR-129	V\$OCT1_07	TF2mir	diamond to cluster40_hsa-mir-129-2 via NM_001001419 (V\$SMAD_Q6_01)
hsa-miR-24	V\$OCT1_B	NO	diamond to cluster129_hsa-mir-23a via NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-194	V\$OCT_C	NO	diamond to cluster43_hsa-mir-194-2 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-214	V\$OCT_C	NO	diamond to cluster17_hsa-mir-199a-2 via NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-302c-star	V\$OCT_C	TF2mir	diamond to cluster201_hsa-mir-302b via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-24	V\$OCT_Q6	NO	diamond to cluster129_hsa-mir-23a via NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)NM_004599 (V\$REBP_Q3)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)NM_005920 (V\$MEF2_Q6_01)
hsa-miR-30a-3p	V\$OCT_Q6	TF2mir mir2TF	diamond to cluster224_hsa-mir-30a via NM_000458 (V\$HNF1_Q6 V\$HNF1_Q6_01)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-199a	V\$PAX2_01	TF2mir	diamond to cluster128_hsa-mir-199a-1 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-199a	V\$PAX6_Q2	TF2mir	diamond to cluster17_hsa-mir-199a-2 via NM_012183 (V\$FOX D3_01 V\$FOX_Q2)
hsa-miR-19b	V\$PAX6_Q2	TF2mir	diamond to cluster292_hsa-mir-106a via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-29b	V\$PAX6_Q2	NO	diamond to cluster21_hsa-mir-29b-2 via NM_012183 (V\$FOX D3_01 V\$FOX_Q2)
hsa-miR-29c	V\$PAX6_Q2	NO	diamond to cluster21_hsa-mir-29b-2 via NM_012183 (V\$FOX D3_01 V\$FOX_Q2)
hsa-miR-302a	V\$PAX6_Q2	TF2mir	diamond to cluster201_hsa-mir-302b via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-302c	V\$PAX6_Q2	TF2mir	diamond to cluster201_hsa-mir-302b via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-302d	V\$PAX6_Q2	TF2mir	diamond to cluster201_hsa-mir-302b via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-302a	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOX O4_01 V\$FOX O4_02 V\$FOX_Q2)

hsa-miR-302b	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-302c	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-302d	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-28	V\$PITX2_Q2	NO	diamond to cluster191_hsa-mir-28 via NM_005253 (V\$AP1_Q2_01)
hsa-miR-212	V\$POU1F1_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_000376 (V\$DR3_Q4 V\$VDR_Q3 V\$VDR_Q6)NM_003221 (V\$AP2_Q3 V\$AP2_Q6 V\$AP2_Q6_01)NM_005239 (V\$ETS2_B V\$ETS_Q4)
hsa-miR-143	V\$POU3F2_01	NO	diamond to cluster212_hsa-mir-143 via NM_012183 (V\$FOX_D3_01 V\$FOX_Q2)
hsa-miR-208	V\$POU3F2_01	NO	diamond to cluster72_hsa-mir-208 via NM_001674 (V\$ATF3_Q6 V\$CREBATF_Q6)
hsa-miR-218	V\$POU3F2_01	mir2TF	diamond to cluster216_hsa-mir-218-2 via NM_001253 (V\$CDC5_01)
hsa-miR-23a	V\$POU3F2_02	NO	diamond to cluster129_hsa-mir-23a via NM_001621 (V\$AHRARNT_01 V\$AHRARNT_02 V\$AHR_01 V\$AHR_Q5)NM_002398 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02 V\$MEIS1_01)
hsa-miR-26a	V\$POU3F2_02	NO	diamond to cluster177_hsa-mir-26a-1 via NM_002955 (V\$RREB1_01)NM_004852 (V\$HNF6_Q6)
hsa-miR-101	V\$POU6F1_01	NO	diamond to cluster263_hsa-mir-101-2 via NM_003150 (V\$STAT3_01 V\$STAT_01 V\$STAT_Q6)NM_005654 (V\$COUP_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-10a	V\$POU6F1_01	TF2mir	diamond to cluster111_hsa-mir-10a via NM_003106 (V\$SOX_Q6)
hsa-miR-186	V\$POU6F1_01	NO	diamond to cluster7_hsa-mir-186 via NM_002142 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02)
hsa-miR-19a	V\$POU6F1_01	NO	diamond to cluster70_hsa-mir-17 via NM_007129 (V\$ZIC2_01)
hsa-miR-19b	V\$POU6F1_01	TF2mir	diamond to cluster70_hsa-mir-17 via NM_007129 (V\$ZIC2_01)
hsa-miR-219	V\$POU6F1_01	NO	diamond to cluster220_hsa-mir-219-1 via NM_006626 (V\$ZID_01)
hsa-miR-342	V\$POU6F1_01	NO	diamond to cluster75_hsa-mir-342 via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-196a	V\$PTF1BETA_Q6	NO	diamond to cluster53_hsa-mir-196a-2 via NM_001489 (V\$GCNF_01)
hsa-miR-9-star	V\$PTF1BETA_Q6	NO	diamond to cluster14_hsa-mir-9-1 via NM_001489 (V\$GCNF_01)

hsa-miR-23a	V\$RFX_Q6	TF2mir	diamond to cluster129_hsa-mir-23a via NM_002229 (V\$AP1_01 V\$AP1_Q2_01)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-28	V\$RFX_Q6	NO	diamond to cluster191_hsa-mir-28 via NM_002229 (V\$AP1_01 V\$AP1_Q2_01)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-182	V\$RORA1_01	NO	diamond to cluster242_hsa-mir-183 via NM_006942 (V\$SOX_Q6)
hsa-miR-181c	V\$RORA2_01	NO	diamond to cluster130_hsa-mir-181c via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-196a	V\$S8_01	NO	diamond to cluster112_hsa-mir-196a-1 via NM_003202 (V\$LEFTCF1_Q4)
hsa-miR-218	V\$S8_01	TF2mir	diamond to cluster216_hsa-mir-218-2 via NM_004498 (V\$HNF6_Q6)
hsa-miR-33	V\$S8_01	NO	diamond to cluster104_hsa-mir-33b via NM_005654 (V\$COUP_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-128b	V\$SMAD4_Q6	NO	diamond to cluster176_hsa-mir-128b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-103	V\$SOX_Q6	NO	diamond to cluster215_hsa-mir-103-1 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-148b	V\$SOX_Q6	mir2TF	diamond to cluster55_hsa-mir-148b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-28	V\$SOX_Q6	NO	diamond to cluster191_hsa-mir-28 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302a	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302b	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302c	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302d	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-129	V\$SP3_Q3	mir2TF	diamond to cluster40_hsa-mir-129-2 via NM_005920 (V\$MEF2_Q6_01)
hsa-miR-302d	V\$SP3_Q3	mir2TF	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-142-5p	V\$SPZ1_01	NO	diamond to cluster113_hsa-mir-142 via NM_002049 (V\$GATA1_01 V\$GATA1_02 V\$GATA1_03 V\$GATA1_04 V\$GATA1_05 V\$GATA_C)
hsa-miR-17-5p	V\$SPZ1_01	NO	diamond to cluster70_hsa-mir-17 via NM_002131 (V\$HMG1Y_Q3)
hsa-miR-	V\$SPZ1_01	NO	diamond to cluster70_hsa-mir-17 via NM_002131 (V\$HMG1Y_Q3)

20a			
hsa-miR-20b	V\$SPZ1_01	NO	diamond to cluster292_hsa-mir-106a via NM_003466 (V\$PAX8_01 V\$PAX8_B V\$PAX_Q6)
hsa-miR-199a	V\$SREBP_Q3	NO	diamond to cluster17_hsa-mir-199a-2 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-19b	V\$SRF_Q6	NO	diamond to cluster292_hsa-mir-106a via NM_001965 (V\$KROX_Q6 V\$NGFIC_01)
hsa-miR-141	V\$TATA_01	NO	diamond to cluster50_hsa-mir-200c via NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)
hsa-miR-23a	V\$TATA_C	NO	diamond to cluster129_hsa-mir-23a via NM_004364 (V\$CEBPA_01 V\$CEBP_01 V\$CEBP_C V\$CEBP_Q2 V\$CEBP_Q2_01 V\$CEBP_Q3 V\$CHOP_01)
hsa-miR-199a	V\$TCF11MAFG_01	mir2TF	diamond to cluster128_hsa-mir-199a-1 via NM_015859 (V\$TFIIA_Q6)
hsa-miR-9-star	V\$TCF11MAFG_01	NO	diamond to cluster14_hsa-mir-9-1 via NM_006237 (V\$OCT_Q6)
hsa-miR-33	V\$TCF1P_Q6	NO	diamond to cluster104_hsa-mir-33b via NM_003204 (V\$MAF_Q6_01 V\$TCF11MAFG_01 V\$TCF11_01)
hsa-miR-106b	V\$TEF_Q6	NO	diamond to cluster238_hsa-mir-106b via NM_001453 (V\$FREAC3_01)
hsa-miR-132	V\$TEF_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_001453 (V\$FREAC3_01)
hsa-miR-212	V\$TEF_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_001453 (V\$FREAC3_01)
hsa-miR-132	V\$TEL2_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)NM_003670 (V\$DEC_Q1)
hsa-miR-212	V\$TEL2_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)NM_003670 (V\$DEC_Q1)
hsa-miR-331	V\$TFIIA_Q6	NO	diamond to cluster63_hsa-mir-331 via NM_000457 (V\$COUP_01 V\$DR1_Q3 V\$HNF4ALPHA_Q6 V\$HNF4_01 V\$HNF4_01_B V\$HNF4_DR1_Q3)
hsa-miR-10a	V\$TFIII_Q6	NO	diamond to cluster111_hsa-mir-10a via NM_007084 (V\$SOX_Q6)
hsa-miR-331	V\$TFIII_Q6	NO	diamond to cluster63_hsa-mir-331 via NM_000457 (V\$COUP_01 V\$DR1_Q3 V\$HNF4ALPHA_Q6 V\$HNF4_01 V\$HNF4_01_B V\$HNF4_DR1_Q3)
hsa-miR-194	V\$TST1_01	NO	diamond to cluster43_hsa-mir-194-2 via NM_000278 (V\$PAX2_01 V\$PAX_Q6)

hsa-miR-92	V\$TST1_01	TF2mir	diamond to cluster12_hsa-mir-92b via NM_002198 (V\$IRF1_01 V\$IRF_Q6 V\$IRF_Q6_01) NM_003152 (V\$STAT5A_01 V\$STAT5A_02 V\$STAT_01 V\$STAT_Q6) NM_012448 (V\$STAT5B_01 V\$STAT_01 V\$STAT_Q6)
hsa-miR-194	V\$YY1_Q6	NO	diamond to cluster23_hsa-mir-194-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)

Table 14 herein below lists pairs of indirect FFLs in the PicTar database taking 5 kb regulatory regions for protein coding genes.

Table 14

<i>miR</i>	<i>TF</i>	<i>has a regular FFL</i>	<i>indirect FFL information</i>
hsa-miR-30a-5p	V\$AFP1_Q6	TF2mir	diamond to cluster224_hsa-mir-30a via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-9-star	V\$AFP1_Q6	NO	diamond to cluster14_hsa-mir-9-1 via NM_006237 (V\$OCT_Q6)
hsa-miR-92	V\$AHRARNT_02	NO	diamond to cluster70_hsa-mir-17 via NM_002131 (V\$HMGIIY_Q3)
hsa-miR-145	V\$AIRE_02	NO	diamond to cluster212_hsa-mir-143 via NM_012183 (V\$FOX D3_01 V\$FOX_Q2)
hsa-miR-132	V\$API_Q4	TF2mir	diamond to cluster101_hsa-mir-212 via NM_001186 (V\$BACH1_01 V\$MAF_Q6_01)
hsa-miR-212	V\$API_Q4	TF2mir	diamond to cluster101_hsa-mir-212 via NM_001186 (V\$BACH1_01 V\$MAF_Q6_01)
hsa-miR-96	V\$ATF1_Q6	NO	diamond to cluster242_hsa-mir-183 via NM_002918 (V\$EFC_Q6 V\$RFX1_01 V\$RFX1_02 V\$RFX_Q6)
hsa-miR-1	V\$ATF_B	NO	diamond to cluster122_hsa-mir-1-2 via NM_005920 (V\$MEF2_Q6_01)
hsa-miR-206	V\$ATF_B	NO	diamond to cluster222_hsa-mir-206 via NM_005920 (V\$MEF2_Q6_01)
hsa-miR-324-5p	V\$CART1_01	NO	diamond to cluster103_hsa-mir-324 via NM_002015 (V\$FOX O1_02 V\$FOX_Q2)
hsa-miR-129	V\$CDP_02	TF2mir	diamond to cluster40_hsa-mir-129-2 via NM_004599 (V\$SRBP_Q3) NM_005587 (V\$AMEF2_Q6 V\$HMEF2_Q6 V\$MEF2_01 V\$MEF2_02 V\$MEF2_03 V\$MEF2_04 V\$MEF2_Q6_01 V\$MMEF2_Q6)

hsa-miR-153	V\$CDP_02	NO	diamond to cluster150_hsa-mir-153-1 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-132	V\$CEBP_Q2	NO	diamond to cluster101_hsa-mir-212 via NM_003220 (V\$AP2_Q3 V\$AP2_Q6 V\$AP2_Q6_01)
hsa-miR-212	V\$CEBP_Q2	NO	diamond to cluster101_hsa-mir-212 via NM_003220 (V\$AP2_Q3 V\$AP2_Q6 V\$AP2_Q6_01)
hsa-miR-9-star	V\$CHX10_01	NO	diamond to cluster14_hsa-mir-9-1 via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-137	V\$CIZ_01	TF2mir	diamond to cluster8_hsa-mir-137 via NM_001452 (V\$FOX_Q2 V\$FREAC2_01)
hsa-miR-186	V\$CREB_Q4	NO	diamond to cluster7_hsa-mir-186 via NM_001489 (V\$GCNF_01)
hsa-miR-183	V\$E2F_Q3	NO	diamond to cluster242_hsa-mir-183 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6) NM_004189 (V\$SOX_Q6)
hsa-miR-93	V\$E2F_Q3_01	TF2mir mir2TF	diamond to cluster238_hsa-mir-106b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-135b	V\$E2F_Q4	NO	diamond to cluster20_hsa-mir-135b via NM_005585 (V\$SMAD_Q6_01)
hsa-miR-7	V\$ETS_Q4	NO	diamond to cluster267_hsa-mir-7-1 via NM_001265 (V\$CDX_Q5)
hsa-miR-129	V\$EVII_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_006195 (V\$PBX_Q3)
hsa-miR-124a	V\$FOXJ2_01	TF2mir	diamond to cluster162_hsa-mir-124a-3 via NM_000457 (V\$COUP_01 V\$DR1_Q3 V\$HNF4ALPHA_Q6 V\$HNF4_01 V\$HNF4_01_B V\$HNF4_DR1_Q3)
hsa-miR-25	V\$FOXJ2_01	NO	diamond to cluster238_hsa-mir-106b via NM_021005 (V\$ARP1_01 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)
hsa-miR-92	V\$FOXJ2_01	TF2mir	diamond to cluster292_hsa-mir-106a via NM_000399 (V\$EGR2_01 V\$EGR_Q6 V\$KROX_Q6) NM_014564 (V\$LHX3_01)
hsa-miR-199a-star	V\$FOXJ2_02	TF2mir	diamond to cluster17_hsa-mir-199a-2 via NM_003199 (V\$TAL1BETAITF2_01)
hsa-miR-129	V\$FOXMI_01	NO	diamond to cluster40_hsa-mir-129-2 via NM_006195 (V\$PBX_Q3)
hsa-miR-128b	V\$FOXO3_01	TF2mir	diamond to cluster176_hsa-mir-128b via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01) NM_012183 (V\$FOXDI3_01 V\$FOX_Q2)
hsa-miR-92	V\$FOXO4_01	NO	diamond to cluster292_hsa-mir-106a via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6) NM_004852 (V\$HNF6_Q6)

hsa-miR-23a	V\$FOXP1_01	NO	diamond to cluster129_hsa-mir-23a via NM_005252 (V\$APIFJ_Q2 V\$API_01 V\$API_Q2_01)
hsa-miR-199a-star	V\$FOX_Q2	TF2mir	diamond to cluster17_hsa-mir-199a-2 via NM_001455 (V\$FOXO3_01 V\$FOX_Q2)
hsa-miR-28	V\$FREAC2_01	NO	diamond to cluster191_hsa-mir-28 via NM_005253 (V\$API_Q2_01)
hsa-miR-194	V\$FREAC3_01	NO	diamond to cluster43_hsa-mir-194-2 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)NM_006164 (V\$MAF_Q6_01 V\$NRF2_Q4)
hsa-miR-29a	V\$GATA1_04	NO	diamond to cluster244_hsa-mir-29b-1 via NM_006163 (V\$MAF_Q6_01 V\$NFE2_01)
hsa-miR-182	V\$HIF1_Q3	NO	diamond to cluster242_hsa-mir-183 via NM_003108 (V\$SOX_Q6)
hsa-miR-153	V\$HIF1_Q5	NO	diamond to cluster150_hsa-mir-153-1 via NM_003106 (V\$SOX_Q6)NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-30a-5p	V\$HIF1_Q5	NO	diamond to cluster224_hsa-mir-30a via NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-30a-5p	V\$HNF3B_01	TF2mir	diamond to cluster224_hsa-mir-30a via NM_021784 (V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-30c	V\$HNF3B_01	NO	diamond to cluster223_hsa-mir-30c-2 via NM_000325 (V\$PITX2_Q2)
hsa-miR-200b	V\$HNF6_Q6	NO	diamond to cluster1_hsa-mir-200b via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-10a	V\$IRF7_01	TF2mir	diamond to cluster111_hsa-mir-10a via NM_002199 (V\$IRF2_01 V\$IRF_Q6 V\$IRF_Q6_01)
hsa-miR-30a-5p	V\$IRF7_01	NO	diamond to cluster224_hsa-mir-30a via NM_012183 (V\$FOXO3_01 V\$FOX_Q2)
hsa-miR-215	V\$IRF_Q6	NO	diamond to cluster23_hsa-mir-194-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)
hsa-miR-23a	V\$IRF_Q6	mir2TF	diamond to cluster129_hsa-mir-23a via NM_000438 (V\$PAX3_01 V\$PAX3_B V\$PAX_Q6)
hsa-miR-23b	V\$IRF_Q6	mir2TF	diamond to cluster269_hsa-mir-23b via NM_001913 (V\$CDPCR1_01 V\$CDPCR3HD_01 V\$CDPCR3_01 V\$CDP_01 V\$CDP_02)
hsa-miR-30a-5p	V\$IRF_Q6	mir2TF	diamond to cluster224_hsa-mir-30a via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-30c	V\$IRF_Q6	mir2TF	diamond to cluster223_hsa-mir-30c-2 via NM_000325 (V\$PITX2_Q2)
hsa-miR-	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)

302a			
hsa-miR-302b	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-302c	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-302d	V\$ISRE_01	NO	diamond to cluster201_hsa-mir-302b via NM_182894 (V\$CHX10_01)
hsa-miR-200c	V\$LMO2COM_02	NO	diamond to cluster50_hsa-mir-200c via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-29a	V\$LMO2COM_02	NO	diamond to cluster244_hsa-mir-29b-1 via NM_006163 (V\$MAF_Q6_01 V\$NFE2_01)
hsa-miR-29b	V\$LMO2COM_02	NO	diamond to cluster21_hsa-mir-29b-2 via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)NM_006163 (V\$MAF_Q6_01 V\$NFE2_01)NM_172373 (V\$ELF1_Q6)
hsa-miR-29c	V\$LMO2COM_02	NO	diamond to cluster21_hsa-mir-29b-2 via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)NM_006163 (V\$MAF_Q6_01 V\$NFE2_01)NM_172373 (V\$ELF1_Q6)
hsa-miR-30a-3p	V\$MEF2_Q4	NO	diamond to cluster224_hsa-mir-30a via NM_021784 (V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-196a	V\$MMEF2_Q6	TF2mir	diamond to cluster53_hsa-mir-196a-2 via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)NM_006352 (V\$RP58_01)
hsa-miR-194	V\$MRF2_01	NO	diamond to cluster23_hsa-mir-194-1 via NM_002509 (V\$NKX22_01)
hsa-miR-301	V\$MRF2_01	NO	diamond to cluster114_hsa-mir-301 via NM_002142 (V\$MEIS1AHOXA9_01 V\$MEIS1BHOXA9_02)
hsa-miR-135b	V\$MYOD_Q6_01	NO	diamond to cluster20_hsa-mir-135b via NM_000376 (V\$DR3_Q4 V\$VDR_Q3 V\$VDR_Q6)
hsa-miR-129	V\$NKX61_01	TF2mir	diamond to cluster40_hsa-mir-129-2 via NM_001913 (V\$CDPCR1_01 V\$CDPCR3HD_01 V\$CDPCR3_01 V\$CDP_01 V\$CDP_02)
hsa-miR-129	V\$NKX62_Q2	NO	diamond to cluster40_hsa-mir-129-2 via NM_002697 (V\$OCT1_01 V\$OCT1_02 V\$OCT1_03 V\$OCT1_04 V\$OCT1_05 V\$OCT1_06 V\$OCT1_07 V\$OCT1_B V\$OCT1_Q5_01 V\$OCT1_Q6 V\$OCT_C V\$OCT_Q6)
hsa-miR-135a	V\$NRSF_01	NO	diamond to cluster64_hsa-mir-135a-2 via NM_014564 (V\$LHX3_01)
hsa-miR-132	V\$OCT1_06	NO	diamond to cluster101_hsa-mir-212 via NM_005252 (V\$AP1FJ_Q2 V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-212	V\$OCT1_06	NO	diamond to cluster101_hsa-mir-212 via NM_005252 (V\$AP1FJ_Q2 V\$AP1_01 V\$AP1_Q2_01)
hsa-	V\$OCT1_06	TF2mir	diamond to cluster191_hsa-mir-28 via

miR-28			NM_005252 (V\$AP1FJ_Q2 V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-141	V\$OCT1_07	NO	diamond to cluster50_hsa-mir-200c via NM_004348 (V\$AML_Q6 V\$PEBP_Q6)
hsa-miR-199a-star	V\$OCT_C	NO	diamond to cluster17_hsa-mir-199a-2 via NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)NM_004496 (V\$HNF3ALPHA_Q6 V\$HNF3_Q6 V\$HNF3_Q6_01)
hsa-miR-24	V\$OCT_Q6	NO	diamond to cluster129_hsa-mir-23a via NM_003131 (V\$SRF_01 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_01 V\$SRF_Q5_02 V\$SRF_Q6)NM_004599 (V\$SREBP_Q3)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)NM_005920 (V\$MEF2_Q6_01)
hsa-miR-30a-3p	V\$OCT_Q6	TF2mir mir2TF	diamond to cluster224_hsa-mir-30a via NM_000458 (V\$HNF1_Q6 V\$HNF1_Q6_01)NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-199a	V\$PAX6_Q2	TF2mir	diamond to cluster128_hsa-mir-199a-1 via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-302a	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-302b	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-302d	V\$PBX1_01	NO	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02 V\$FOX_Q2)
hsa-miR-199a-star	V\$POU3F2_01	NO	diamond to cluster17_hsa-mir-199a-2 via NM_003107 (V\$SOX_Q6)NM_012183 (V\$FOX_D3_01 V\$FOX_Q2)
hsa-miR-26a	V\$POU3F2_02	NO	diamond to cluster177_hsa-mir-26a-1 via NM_002955 (V\$RREB1_01)
hsa-miR-10a	V\$POU6F1_01	TF2mir	diamond to cluster111_hsa-mir-10a via NM_003106 (V\$SOX_Q6)
hsa-miR-23a	V\$RFX_Q6	TF2mir	diamond to cluster129_hsa-mir-23a via NM_005354 (V\$AP1_01 V\$AP1_Q2_01)
hsa-miR-92	V\$RFX_Q6	TF2mir mir2TF	diamond to cluster292_hsa-mir-106a via NM_000280 (V\$PAX6_01 V\$PAX6_Q2 V\$PAX_Q6)
hsa-miR-302a	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302b	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-302c	V\$SOX_Q6	NO	diamond to cluster201_hsa-mir-302b via NM_005604 (V\$BRN2_01 V\$OCT_Q6 V\$POU3F2_01 V\$POU3F2_02)
hsa-miR-129	V\$SP3_Q3	mir2TF	diamond to cluster40_hsa-mir-129-2 via NM_005920 (V\$MEF2_Q6_01)
hsa-miR-	V\$SP3_Q3	mir2TF	diamond to cluster201_hsa-mir-302b via NM_005938 (V\$FOXO4_01 V\$FOXO4_02

302c			V\$FOX_Q2)
hsa-miR-142-5p	V\$SPZ1_Q1	NO	diamond to cluster113_hsa-mir-142 via NM_002049 (V\$GATA1_Q1 V\$GATA1_Q2 V\$GATA1_Q3 V\$GATA1_Q4 V\$GATA1_Q5 V\$GATA_C)
hsa-miR-199a	V\$SREBP_Q3	NO	diamond to cluster17_hsa-mir-199a-2 via NM_000346 (V\$SOX9_B1 V\$SOX_Q6)
hsa-miR-141	V\$TATA_Q1	NO	diamond to cluster50_hsa-mir-200c via NM_003131 (V\$SRF_Q1 V\$SRF_C V\$SRF_Q4 V\$SRF_Q5_Q1 V\$SRF_Q5_Q2 V\$SRF_Q6)
hsa-miR-199a	V\$TCF11MAFG_Q1	mir2TF	diamond to cluster128_hsa-mir-199a-1 via NM_015859 (V\$TFIIA_Q6)
hsa-miR-132	V\$TEL2_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_003670 (V\$DEC_Q1)
hsa-miR-212	V\$TEL2_Q6	NO	diamond to cluster101_hsa-mir-212 via NM_003670 (V\$DEC_Q1)
hsa-miR-10a	V\$TFIII_Q6	NO	diamond to cluster111_hsa-mir-10a via NM_007084 (V\$SOX_Q6)
hsa-miR-219	V\$TFIII_Q6	NO	diamond to cluster276_hsa-mir-219-2 via NM_003367 (V\$USF_Q6 V\$USF_Q6_Q1)
hsa-miR-93	V\$TFIII_Q6	NO	diamond to cluster238_hsa-mir-106b via NM_005654 (V\$COUP_Q1 V\$COUP_DR1_Q6 V\$DR1_Q3 V\$DR4_Q2)NM_005693 (V\$DR4_Q2 V\$LXR_Q3)
hsa-miR-194	V\$TST1_Q1	NO	diamond to cluster43_hsa-mir-194-2 via NM_000278 (V\$PAX2_Q1 V\$PAX_Q6)
hsa-miR-194	V\$YY1_Q6	NO	diamond to cluster23_hsa-mir-194-1 via NM_000176 (V\$GRE_C V\$GR_Q6 V\$PR_Q2)

Expression Analyses Supports miR-TF and miR-miR Predicted Regulatory

Interactions: Next, the expression profiles of TF-miR partners were analyzed. Expression data across human tissues and organs has recently become available for miRs [Barad O, et al. (2004) Genome Res 14: 2486-2494] and is also available for protein coding mRNAs [Su AI, et al. (2004) Proc Natl Acad Sci U S A 101: 6062-6067]. Fortunately, for all the five healthy tissues (brain, liver, thymus, testes, and placenta) for which miRs expression was assayed, mRNAs were measured too. Thus the correlation coefficient was calculated between the expression profiles of each mRNA and each miR, and in particular between all TF-miR partners. For background statistics, correlations were first calculated between all pairs of miRs and TFs in the expression dataset (i.e., not necessarily the TF-miR partners identified above) and their distribution was obtained. It was found, as may be expected, a distribution that is centered on zero (Figure 5A). On this background the distribution of

correlation coefficients between expression profiles of TF–miR partner pairs are shown (Figure 5B and 5C). Strikingly, it was found that TF–miR partner pairs tended to have high correlation coefficients between them, but curiously, there was also a tendency for strong negative correlations in some of these pairs. These two tendencies were further enhanced when only the TF–miR pairs were inspected that are connected through an FFL. Given that some TFs can act as activators and others as repressors, and given that miRs may act at the level of translation inhibition or transcript degradation, both negative and positive correlations between TF–miR partners may be mechanistically rationalized.

The same miR tissue expression data was further used to shed light on the co-occurrence and avoidance of miR pairs. Pairs of miRs were tested that are either highly correlated in their expression levels or anticorrelated to each other across human samples have particularly high co-occurrence or avoidance *p*-values. An encouraging correspondence was found, whereby miR pairs that were positively correlated in expression had a significant tendency for high co-occurrence, whereas miRs with negative correlation in tissue expression typically tended to deliberately avoid residing in shared 3' UTRs. These observations provide experimental support for miR pairs and TF–miR regulatory interactions that were initially predicted based on sequence information alone.

DISCUSSION

The present example provides a comprehensive characterization of both global and local structural properties of the network of combinatorial regulatory interactions spanned by miRs and TFs. Extensive interactions were discovered between miRs and between miRs and TFs, and it was realized that thousands of human genes are subject to their regulatory effects. Inspection of the distributions of predicted miR sites in human genes' 3' UTRs revealed hundreds of target hubs in the human genome, genes that appear to be controlled by multiple regulators — miRs in the present case. Curiously, the current target hubs show highly nonrandom representation of specific gene functionalities. Particularly, genes related to development and genes that regulate transcription are enriched among the set of target hubs. These findings constitute another demonstration of the recent concept [Borneman AR, et al. (2006) *Genes Dev* 20: 435–448] that suggests that genes that exert extensive regulation on crucial processes are themselves often heavily regulated. So far this has been discussed in the context of the yeast transcription network; this study extends the scope of this concept to the case of miRs in mammalian genomes. In addition, given that each method of target prediction has its own rate of false positives, target hubs, which

are predicted to be targeted by multiple miRs, are more likely to actually represent true targets of miR silencing.

The network of extensive regulatory interactions observed here between transcriptional regulators (TFs) and post-transcriptional regulators (miRs), is another interesting global feature. Altogether it was estimated that the number of human genes that are under combined regulation at the transcriptional and posttranscriptional silencing levels is between ~1,000 and ~4,000 (i.e., ~12 % to ~43 % of the ~9,000 analyzed genes, according to the TargetScan and PicTar networks, respectively). Overall ~9,000 genes were included in the present analyses, these are genes that are currently predicted to have at least one binding site for a known miR. Considering the fact that the collection of mammalian miRs is yet incomplete, and the fact that human specific miRs were not included in the analysis, it can be anticipated that the true number of human genes that are subject to a dual TF-miR regulation was underestimated in this study. For comparison, it was recently estimated that in the *Saccharomyces cerevisiae* genome about 13 % of the genes are subject to regulation at the combined transcriptional and posttranscriptional level, albeit with different mechanisms of posttranscriptional regulation operating in this organism, which does not have the miR silencing pathway.

The present inventors also examined local properties of the regulatory network, the network motifs. The network motifs described here are different from those originally described [Mangan S, Alon U (2003); Proc Natl Acad Sci U S A 100: 11980–11985; Milo R, et al. (2002) Science 298: 824–827; Shen-Orr SS, (2002) Nat Genet 31: 64–68] in that they are composed of a TF and a miR instead of two TFs, as in the original case. It has been shown here that network motifs are not only significantly abundant, but also that, according to their current definition, each of them is involved in the regulation of large set of targets. Interestingly, TF and miR pairs that participate in network motifs show a significant tendency towards high tissue expression correlations or anticorrelations of the two regulators, providing essential experimental support to combinations predicted solely based on sequence information.

Motifs in which the miR regulates its partner TF constitute a type II coherent FFL [Mangan S, Alon U (2003) Proc Natl Acad Sci U S A 100: 11980–11985]. In this case it seems that a miR that silences a set of genes posttranscriptionally also silences the transcriptional regulator of these genes, presumably to also prevent de novo transcription of its target genes. This design may be used to minimize leaky transcription of genes in

space and time when their expression is undesired. For example, this mechanism could be useful in determining developmental fate in differentiation boundaries.

The motifs in which the TF has a binding site in the promoter of its partner miR corresponds to the incoherent type I FFL (assuming that the TF is a positive regulator).
 5 Interestingly, in the *S. cerevisiae* transcription network this circuit is the second most highly abundant FFL [Mangan S, Alon U (2003) Proc Natl Acad Sci U S A 100: 11980–11985]. An intriguing question is what may be the reason for the observed abundance of this circuit in which a TF regulates its partner miR? On the face of it, such regulation appears wasteful if the TF is a positive regulator, since the TF activates an entire set of
 10 genes and also a miR that may shut those target genes down. However, if a temporal gap in the activation time of the target genes and the miR exists, then the circuit may be utilized for useful regulatory purposes. For instance if the TF activates first the target genes and only later the miR (e.g., due to higher affinity, during a process in which the TF's concentration builds up, the activation of the miR may be timed to obtain a desired delayed
 15 shutdown of the regulated genes. Similar wiring in the cases of antisense RNAs, another type of regulatory transcripts, and TFs that regulate them in conjunction with their overlapping sense transcripts have also been considered. The opposite situation, in which the TF positively activates the miR first and only later the target gene, may also be of interest as it can act as a buffer for noisy fluctuations in the levels of the targets; as long as
 20 the mRNA level of the target gene is below the inhibition capacity of the miR, fluctuations in its expression levels would not be further propagated. Further, in cases where the miR works predominantly as a translation inhibitor, a controlled mechanism for “just in time” translation for multiple genes is needed for certain functionalities. For example, the miR translation inhibition mechanism was suggested to facilitate localized translation in
 25 mammalian dendrites, and to play a crucial role in synaptic plasticity. Such a circuit of coregulating TF–miR in an FFL, where the miR is transcribed by the TF in parallel to the set of mutual targets, could function in featuring localized translation to a whole pathway of regulated genes. Interestingly though, an example of one indirect FFL can be pointed out, where a brain related TF, CREB (CREBATF), partners with a miR that is known to be
 30 expressed in the brain, miR-125b. CREBATF was predicted to regulate miR-125b through STAT3, which interestingly is also within the list of mutual targets of both miR125b and CREBATF, indicating an even more complex design.

One of the FFLs that came out of the present analysis is a composite loop in which the TF regulates the miR and the miR appears to regulate the TF (i.e., a TF $\leftrightarrow$ miR

motif). The circuit consists of the TF E2F and miR-93. miR-93 is part of a cluster of three miRs, miR-106b, miR-93 and miR-25, which lie in close proximity to each other inside an intron of the *MCM7* gene. This network motif was found as an FFL TF→miR in the TargetScan network and as a composite loop in the PicTar network, where all three miRs in the cluster were predicted to target E2F (specifically E2F1 and E2F3). miR-93 cluster members are also homologous to two other genomic miR clusters, one of which is miR cluster 17/92. Recent evidence suggests a tight regulatory connection of cluster miR-17/92 and E2F. E2F1, 2, and 3 were shown to directly upregulate the expression of the miRs encoded in this cluster, while these miRs in turn were shown to act in a feedback loop and target E2F1-3 mRNAs. It was suggested that this feedback may play a role in the major decision mediated by E2F (induction of cellular proliferation or apoptosis). The present data suggests that this intricate regulatory circuit might have another layer to it; in addition to being targeted by the miR-17/92 cluster, E2F family genes might also be targeted by miR-93 cluster members, which share similar seeds. In turn, the miR-93 cluster is transcribed from an intron of the *MCM7* host gene, which is a verified target of the E2F family. Moreover, here the architecture is more complex, as it also includes a set of mutual target genes, through which E2F and the miR-93 cluster may exert their regulatory roles.

EXAMPLE 3

p53-repressed miRNAs are involved with E2F in a Feed Forward Loop promoting proliferation

MATERIALS AND METHODS

Cell culture: WI-38, MRC5, IMR90 (Obtained from the ATCC), and PFCA179 cells were cultured in MEM with 10 % FCS, 1 mM sodium pyruvate, 2 mM L-glutamine, and antibiotics. U2OS and H1299 cell lines were cultured in DMEM and RPMI, respectively, with 10 % FCS and antibiotics. MCF10A cells were maintained in DMEM F12 supplemented with 5 % horse serum, 0.5 µg/ml hydrocortisone, 0.1 mg/ml insulin, 0.1 µg/ml cholera toxin, and 10 ng/ml EGF. All cells were maintained in a humidified incubator at 37 °C and 5 % CO₂. Primary fibroblasts were passaged every 5-6 days. PDLs were calculated using the formula: PDLs=log[cell output/cell input]/log2. For colony formation assays, 1x10³ cells were seeded in 100 mm dishes, grown for 14 days and stained with crystal violet.

Plasmids and retroviral infections: GSE56 was subcloned from pBabe-GSE56-puro (Ossovskaya et al, 1996, Proc Natl Acad Sci U S A 93: 10309-10314) into pLXSN-Neo. Small hairpin RNAs (shRNAs) targeting p53 (p53i) or mouse NOXA (Control shRNA) were stably expressed using pRetroSuper (Berkovich and Ginsberg, 2003, Oncogene 22: 161-167). ER-E2F1 was described in (Vigo et al, 1999, Mol Cell Biol 19: 6379-6395). E1A was expressed from pBabe-puro-E1A12S. For expression of miR-106b/93/25, a 1 kb human genomic fragment was cloned with the primers 5'-ggatcctatcctgcgcctttcc-3' (SEQ ID NO: 1) and 5'-cacatggccacagaagac-3' (SEQ ID NO: 2) into miR-Vec (Voorhoeve et al, 2006, Cell 124: 1169-1181). Retrovirus infection procedures were described in (Milyavsky et al, 2003, Cancer Res 63: 7147-7157).

RNA preparation and quantitative real-time PCR (QRT-PCR): RNA was extracted with TRI-Reagent (Molecular Research Center, Inc.). For mRNA quantification, a 2 µg aliquot of total RNA was reverse transcribed using Bio-RT (BIO LAB) and random hexamers. QRT-PCR was performed using Platinum SYBR Green qPCR SuperMix (invitrogen). mRNAs levels were normalized to GAPDH. Primer sequences are listed in Table 15 herein below. For miRNA quantification, TaqMan miRNA assays (Applied Biosystems) were used according to manufacturer protocol. Levels were normalized to the U6 control. All QRT-PCR reactions were performed on ABI7300 machine. Results are presented as mean and standard deviation for two duplicate runs.

Table 15

<i>Gene Symbol</i>	<i>Forward Primer (5' to 3')</i>	<i>Reverse Primer (5' to 3')</i>
GAPDH	Agcctcaagatcatcagcaatg (SEQ ID NO: 3)	Cacgataccaaagtgtcatggat (SEQ ID NO: 4)
MCM7	Tctggcacgtctgagaatggt (SEQ ID NO: 5)	Acggacggtggcaaatatca (SEQ ID NO: 6)
C13ORF25	Gaagatggtggcggctactc (SEQ ID NO: 7)	Ggtgcagttaggtccacgtgtat (SEQ ID NO: 8)
E2F1	Ccatccaggaaaagggtgaa (SEQ ID NO: 9)	Agcgcttggtggtcagattc (SEQ ID NO: 10)
CCNE1 (Cyclin E)	Tttacccaaactcaacgtgcaa (SEQ ID NO: 11)	Tcggagacctaccagttatta (SEQ ID NO: 12)
CDKN1A (p21)	Cgcgactgtgatgcgctaag (SEQ ID NO: 13)	Ggaacctctcattcaaccgcc (SEQ ID NO: 14)
CDKN1C (p57)	Gaacgccgaggaccagaac (SEQ ID NO: 15)	Ggcatgtcctgctggaagtc (SEQ ID NO: 16)
RBL2 (p130)	Caagcaacctcagccttcca (SEQ ID NO: 17)	Ttctctccatctaaagttaccgaaga (SEQ ID NO: 18)
CDKN1B (p27)	Gaagcactgcagagacatggaa (SEQ ID NO: 19)	Ctgcccttctccacctcttg (SEQ ID NO: 20)
CDC20	Gagggtggctgggtcctct	Cagatgcgaatgtgtcgatca

	(SEQ ID NO: 21)	(SEQ ID NO: 22)
TP53	Cccaagcaatggatgattga (SEQ ID NO: 23)	Ggcattctgggagcttcatt (SEQ ID NO: 24)
BIC	Tgtgcgagcagagaatctacctt (SEQ ID NO: 25)	Tggaggaagaacaggcttagaa (SEQ ID NO: 26)
DHFR	Gtctggatagttggtggcagttc (SEQ ID NO: 27)	Tgggtgattcatggcttcct (SEQ ID NO: 28)

miRNA microarrays, data analysis and clustering: The miRNA profiling presented in figure 1A was performed as follows: RNA was extracted from WI-38 cells using TRI-Reagent as described above, labeled with Hy5 and hybridized on Exiqon's miRCURY™ LNA Array (v.8.1) with a common reference Hy3-labeled RNA pool. Two biological replicates were performed for each sample type. Hy5/Hy3 ratios were log2 transformed and filtered such that miRs which were undetected in 11 or 12 samples were discarded. Duplicates were averaged, such that each miR was represented by six values, corresponding to the six different samples. For each miR, a credibility value was calculated as one minus the average of the six standard deviations (SD) between the duplicates. A duplicate that had one missing value was set as the detected value and was assigned with high SD. The 5 % most non-credible miRs were discarded. Data was clustered using hierarchical clustering (average linkage), with 20 clusters.

Analysis of miRNA targets expression coherence: The entire set of miRNA expression profiles was clustered into 20 clusters based on the above expression data (WI-38 young vs. senescent, along with p53 inactivation). Then, a set of predicted target for the miRs from each cluster using PicTar was compiled (Krek et al, 2005, Nat Genet 37: 495-500). Specifically, for each of the 20 miR clusters a series of potential sets of targets was created. The first set consisted of mRNAs predicted to be targeted by at least one miR from the cluster. The second set consisted of mRNAs predicted to be targeted by at least two miRs from the cluster, and so on. The expression coherence (EC) score, a measure of expression similarity (Pilpel *et al*, 2001, Nat Genet 29: 153-159), was then computed for each set of targets according to their expression described in Milyavsky *et al*. (2005), Cancer Res 65: 4530-4543. The most significantly coherent expression pattern belonged to the set of genes that had target sites for at least five miRs from the 'p53-repressed miR cluster' (EC p-value = 5x10⁻³).

Immunoblot analysis: Western blots were performed as described in (Milyavsky *et al*, 2005, Cancer Res 65: 4530-4543). The following antibodies were used: α-p53 pAb H-47, α-p21 sc-377 (Santa Cruz), α-E2F1 sc-193 (Santa Cruz), α-GAPDH MAB374

(Chemicon), α -p130 sc-317 (Santa Cruz), α -p57 sc-8298 (Santa Cruz), α -pRb 554136 (Pharmingen), α - β -tubulin T7816 (Sigma).

Cell-cycle analysis: Cells were labeled for 30 minutes with 10 μ M BrdU (Sigma), fixed with 70 % EtOH/HBSS (2 hours, -20 °C), treated with 2M HCl/0.5 % Triton, washed and treated with 0.1M Na₂B₄O₇ pH 8.5, and stained with FITC-conjugated anti-BrdU (Becton Dickinson) and 10 μ g/ml propidium iodide. Samples were analyzed using a FACSsort machine (Becton Dickinson). At least 1×10^4 events were recorded per sample.

Senescence-associated beta-galactosidase (SA- β -Gal) activity assay: Cells were fixed with 3 % formaldehyde/PBS for 5 minutes, washed with PBS and incubated for 16 hours at 37 °C with a solution containing 1 mg/ml X-gal/40 mM citric acid, sodium phosphate, pH 6.0/5 mM potassium ferrocyanide/5 mM potassium ferricyanide/150 mM NaCl/2 mM MgCl₂.

RESULTS

In order to identify novel p53-regulated miRs two isogenic cell cultures were established that differ in their p53 status and analyzed their miRNA profiles both under normal conditions as well as in contexts that involve p53 activation. WI-38 primary human fibroblasts were infected with a retrovirus encoding for the p53-inactivating peptide, GSE56 (Ossovskaya et al, 1996, Proc Natl Acad Sci U S A 93: 10309-10314). These cells (GSE) and their active p53 counterparts (Con) were treated with the DNA damaging agent doxorubicin or grown until the onset of replicative senescence (the establishment of the system is depicted in Figures 10A-F). Analysis of miRNA expression patterns revealed several expression clusters (see Materials and Methods). Notable among these was a cluster populated with miRs whose expression was negatively regulated by p53 at basal levels. The cluster showed additional downregulation in senescent cells, which was attenuated upon p53 inactivation. This cluster was named the '*p53-repressed miR cluster*' (Figure 11). Notably, doxorubicin treatment, which resulted in a considerable activation of p53 and its mRNA targets (Figures 10A-F), did not significantly affect the levels of these miRs.

The presented cluster contain families of paralogous cancer-related miRNAs

Some of the miRs represented in the cluster (Figure 11) are transcribed from three homologous genomic loci, previously reported as paralogs that evolved from a common evolutionary origin (Tanzer and Stadler, 2004). These include miR-106b/93/25 that reside within an intron of the cell-cycle gene 'minichromosome maintenance protein 7' (*MCM7*);

miR-17/18a/19a/20a/19b-1/92a-1 (miR-17-92 polycistron) that are transcribed as the non-coding RNA c13orf25; and miR-106a/18b/20b/19b-2/92-2 (miR-106a-92 polycistron) that are clustered on chromosome X. This data indicates that not only were the miRNA sequences and genomic organization conserved during evolution, but also their transcriptional regulation. Another polycistron, comprising miR-15b and miR-16, is also represented in the cluster.

Many members of the cluster are overexpressed in various tumors; consistent with the frequent p53 loss of function in cancer, and some were shown to possess oncogenic functions. For example, miR-106a, miR-17-5p, miR-20a and miR-155, were reported to be commonly overexpressed in solid tumors (Volinia *et al*, 2006, Proc Natl Acad Sci U S A 103: 2257-2261). Members of the miR-17-92 polycistron are overexpressed in lymphomas as well as in lung and colorectal carcinomas and were shown to accelerate tumor growth. Interestingly, the *MCM7* gene that contains three of the clusters' miRs in its intron (miR-106b/93/25) is amplified or overexpressed in diverse types of cancers, as are its resident miRs. Consistently, the miR-106b/93/25 polycistronic members were suggested to promote cell cycle progression. Finally, miR-155 and its host non-coding RNA (BIC) were reported to be specifically overexpressed in several types of B-cell lymphomas and to predict poor prognosis in lung cancer.

Representative miRNAs show p53-dependent repression during senescence in many cell types: To further validate the present data, two additional human isogenic cell culture pairs were generated from IMR90 lung primary fibroblasts and from prostate-cancer associated fibroblasts (CAFs). Each culture was infected with a retrovirus encoding for either a small hairpin RNA targeting p53 (p53i) or a control RNAi (Con), and grown until the onset of replicative senescence. p53 knock-down, which significantly reduced the mRNA and protein levels of both p53 and its target p21, delayed the onset of senescence by approximately ten population doublings (Figure 12A and Figures 13A-D). For these cell types, as well as for the WI-38 cells, the levels of representative miRs were compared using TaqMan miRNA assays. Analyses of miR-106b and miR-17-5p, as well as of their host transcripts *MCM7* and *c13orf25*, respectively, revealed transcriptional repression upon replicative senescence in all three tested cell cultures in a manner that was partially or completely p53-dependent (Figure 12B). Additionally, the non-coding RNA BIC and its resident miR-155 were also transcriptionally repressed in a p53-dependent manner upon replicative senescence (Figure 13D).

The miRNAs are associated with p53 and E2F in a proliferation-related regulatory network: A mRNA '*proliferation cluster*' was previously reported that consists mainly of cell-cycle related genes (Milyavsky et al, 2005, Cancer Res 65: 4530-4543). This cluster emerged from an mRNA profiling of an *in-vitro* transformation process in which primary WI-38 cells were gradually transformed, resulting in tumorigenic cells. Importantly, the '*proliferation cluster*' is one of the most prominent expression signatures revealed when tumors are compared to normal tissues or when highly proliferating cells are compared to slow growing cells, and contains many cell-cycle periodic genes. The expression pattern of the '*proliferation cluster*' is highly similar to that of the '*p53-repressed miR cluster*'; i.e. the '*proliferation cluster*' mRNAs display p53-dependent downregulation. The similarity in expression patterns prompted the present inventors to hypothesize that both clusters share a common transcriptional program. It was previously shown that the p53-mediated repression of the '*proliferation cluster*' was mediated via E2F (Tabach et al, 2005, Mol Syst Biol 1: 2005 0022). Providing further support, a conserved E2F binding site is found upstream of the three polycistronic miRs. Recently, it was shown that the miR-17-92 and the miR-106b/93/25 polycistrons are transcriptionally activated by E2F family members (O'Donnell et al, 2005, Nature 435: 839-843; Petrocca et al, 2008, Cancer Cell 13: 272-286; Sylvestre et al, 2007, J Biol Chem 282: 2135-2143; Woods et al, 2007, J Biol Chem 282: 2130-2134).

In view of all the above, it appears conceivable that these miRs are transcriptionally activated by E2F, and that p53 exerts its repression via E2F inhibition. In agreement with the observed downregulation of the '*p53-repressed miR cluster*' in senescence, it was shown that E2F activity is significantly downregulated in senescent cells (Campisi and d'Adda di Fagagna, 2007, Nat Rev Mol Cell Biol 8: 729-740). In addition, the miRs presented here are proposed to be novel members of the well established '*proliferation cluster*'.

The p53-dependent repression of miRNAs from the cluster is mediated via E2F1: To experimentally test whether the miRs and their host mRNAs are regulated by E2F1 in primary cells, WI-38 cells were infected with a retrovirus encoding for an E2F1 protein fused to a modified estrogen receptor ligand binding domain (ER). Treatment of ER-E2F1 expressing cells with 4-OHT permits ER-E2F1 translocation to the nucleus, thereby inducing its transcriptional activity. As depicted in Figure 14A, following 4-OHT treatment an upregulation of candidate miRNAs and host mRNAs which were part of the cluster were observed and together represent all three paralogous polycistrons.

Specifically, the MCM7 gene and its resident miRNAs miR-106b, miR-93 and miR-25, the non coding RNA c13orf25 and its resident miR-17-5p as well as miR-106a that represents the miR-106a-92 cluster. Upregulation of MCM7 and its resident miRs following 4-OHT treatment was also observed in ER-E2F1 expressing lung carcinoma cells (H1299) and osteosarcoma cells (U2OS) (Figures 15A-B). Next, WI-38 cells were infected with E1A, a viral oncoprotein that disrupts pRb-E2F complexes and leads to an upregulation of the endogenous E2F activity. As expected, E1A overexpression resulted in elevated levels of all the above mentioned representative miRNAs (Figure 14B). Of note, the levels of miR-155, which belongs to the immune response co-cluster, were not affected by E2F activation.

Having shown that representative miRs are activated by E2F1 in the present system, p53-dependent repression was tested to analyze whether it is mediated via modulation of E2F1 activity. To that end, WI-38 cells were infected with a retrovirus encoding for either a small hairpin RNA targeting p53 (p53i) or a control RNAi (Con) and treated them with Nutlin-3, a small molecule that stabilizes the p53 protein by inhibiting its Mdm2-dependent ubiquitylation and degradation. Nutlin treatment resulted in a robust p53 protein accumulation, accompanied by p21 mRNA and protein induction (Figures 16A-B), which was completely abrogated in the p53i cells. Remarkably, E2F1 mRNA and protein levels were downregulated upon Nutlin treatment in a p53-dependent manner. Cyclin E showed a similar pattern, supporting the notion that E2F1 downregulation was accompanied by a reduction in E2F activity. Accordingly, MCM7 and its resident miR-106b were both downregulated in a p53-dependent manner (Figure 16A) along with other miRs from the cluster but not with the immune-response related miR-155 (data not shown). Thus, Nutlin treatment, a non genotoxic p53 activating signal, resulted in a p53-dependent transcriptional repression of mRNAs and miRNAs with associated cell-cycle functions. To substantiate the causal relationship between the p53-dependent reduction of E2F1 activity and the repression of the miRs and their hosts control and E1A expressing WI-38 cells were treated with Nutlin. As depicted in Figures 16C-D, E1A induced the expression and prevented the Nutlin-dependent repression of E2F1 as well as of its target Cyclin E. Most significantly, E1A overexpression abolished the downregulation of MCM7 and miR-106b upon Nutlin treatment. A similar pattern was observed for miR-17-5p and its host c13orf25 (data not shown). It may therefore be concluded that E2F1 repression by p53 is necessary for the downregulation of MCM7 and miR-106b. The same mechanism

may underlie the p53-dependent downregulation of additional miRs from the cluster and, more specifically the three paralogous polycistrons.

The miRNAs target key cell-cycle regulators and affect pivotal characteristics of proliferation:

Next, the present inventors set out to identify the functions of the p53-repressed miRs. The miR-106b/93/25 polycistron was focused on as a representative member of the large family of miRs that includes also the miR-17-92 and miR-106a-92 polycistrons. The genomic region encoding miR-106b, miR-93 and miR-25 was overexpressed, which corresponds to an intron of the *MCM7* gene in young WI-38 cells and in MCF10A mammary epithelial cells, both characterized by low basal expression of these miRs. Following the prediction of E2F and miR-106b/93/25 involvement in a feed forward loop, in which they both target a mutual set of genes (Example 1), a list of their mutual predicted targets was compiled as set forth in Table 16 herein below.

Table 16

RefSeq	Symbol	Name	PicTar predicted sites		
NM_000076	CDKN1C	cyclin-dependent kinase inhibitor 1C	miR-25		
NM_000321	RB1	retinoblastoma 1	miR-93	miR-106b	
NM_001124	ADM	adrenomedullin	miR-25		
NM_001386	DPYSL2	dihydropyrimidinase-like 2	miR-93	miR-106b	
NM_001396	DYRK1A	dual-specificity tyrosine-(Y)-phosphorylation	miR-93	miR-106b	
NM_001430	EPAS1	endothelial PAS domain protein 1	miR-93	miR-106b	
NM_001450	FHL2	four and a half LIM domains 2 isoform 1	miR-25		
NM_001753	CAV1	caveolin 1	miR-106b		
NM_001769	CD9	CD9 antigen	miR-25		
NM_001949	E2F3	E2F transcription factor 3	miR-93	miR-106b	miR-25
NM_002024	FMR1	fragile X mental retardation 1	miR-25		
NM_002499	NEO1	neogenin homolog 1	miR-93		
NM_003016	SFRS2	splicing factor, arginine/serine-rich 2	miR-93	miR-106b	
NM_003139	SRPR	signal recognition particle receptor ('docking	miR-25		
NM_003272	TM7SF1	transmembrane 7 superfamily member 1	miR-106b		
NM_003505	FZD1	frizzled 1	miR-106b		
NM_003954	MAP3K14	mitogen-activated protein kinase kinase kinase	miR-93	miR-106b	
NM_004036	ADCY3	adenylate cyclase 3	miR-25		
NM_004354	CCNG2	cyclin G2	miR-93	miR-106b	
NM_004364	CEBPA	CCAAT/enhancer binding protein alpha	miR-25		
NM_004844	SH3BP5	SH3-domain binding protein 5 (BTK-associated)	miR-93	miR-106b	
NM_005197	CHES1	checkpoint suppressor 1	miR-106b		

NM_005458	GPR51	G protein-coupled receptor 51	miR-106b		
NM_005596	NFIB	nuclear factor I/B	miR-93	miR-25	
NM_005779	LHFPL2	lipoma HMGIC fusion partner-like 2	miR-25		
NM_005923	MAP3K5	mitogen-activated protein kinase kinase kinase	miR-93	miR-106b	
NM_006195	PBX3	pre-B-cell leukemia transcription factor 3	miR-106b		
NM_006352	ZNF238	zinc finger protein 238 isoform 2	miR-93	miR-106b	
NM_006482	DYRK2	dual-specificity tyrosine-(Y)-phosphorylation	miR-93	miR-25	
NM_006751	SSFA2	sperm specific antigen 2	miR-93	miR-106b	miR-25
NM_006806	BTG3	B-cell translocation gene 3	miR-93	miR-106b	
NM_012334	MYO10	myosin X	miR-106b		
NM_014344	FJX1	four jointed box 1	miR-93	miR-106b	
NM_014679	KIAA0092	translokin	miR-93	miR-106b	
NM_014876	KIAA0063	KIAA0063 gene product	miR-93	miR-106b	miR-25
NM_015008	KIAA0779	KIAA0779 protein	miR-93	miR-106b	
NM_015678	NBEA	neurobeachin	miR-93	miR-106b	
NM_016131	RAB10	ras-related GTP-binding protein RAB10	miR-93	miR-106b	
NM_016357	EPLIN	epithelial protein lost in neoplasm beta	miR-93	miR-106b	
NM_017803	FLJ20399	hypothetical protein FLJ20399	miR-25		
NM_021005	NR2F2	nuclear receptor subfamily 2, group F, member 2	miR-106b		
NM_053056	CCND1	cyclin D1	miR-93	miR-106b	
NM_057749	CCNE2	cyclin E2 isoform 1	miR-106b	miR-25	
NM_145725	TRAF3	TNF receptor-associated factor 3 isoform 1	miR-25		
NM_153719	NUP62	nucleoporin 62kDa	miR-93		
NM_173075	APBB2	amyloid beta A4 precursor protein-binding,	miR-93	miR-106b	
NM_173173	NR4A2	nuclear receptor subfamily 4, group A, member 2	miR-93	miR-106b	
NM_173200	NR4A3	nuclear receptor subfamily 4, group A, member 3	miR-93	miR-106b	miR-25
NM_174886	TGIF	TG-interacting factor isoform d	miR-25		
NM_181659	NCOA3	nuclear receptor coactivator 3 isoform a	miR-93	miR-106b	
NM_182744	NBL1	neuroblastoma, suppression of tumorigenicity 1	miR-93	miR-106b	
NM_183384	RNF13	ring finger protein 13 isoform 3	miR-106b		
NM_197968	ZNF198	zinc finger protein 198	miR-93		
NM_198966	PTH1H	parathyroid hormone-like hormone isoform 1	miR-93	miR-106b	
NM_199334	THRA	thyroid hormone receptor, alpha isoform 1	miR-93	miR-106b	
NM_024322	MGC11266	hypothetical protein MGC11266	miR-93	miR-106b	

Interestingly, many of these predicted targets participate in cell-cycle regulation (p-value for "cell cycle" annotation= 1.4×10^{-10}). The protein levels of selected predicted targets in the miR-106b/93/25 overexpressing cells were measured (Figures 17A-D). A downregulation of p21, was observed, as well as of pRB and p130, which were previously suggested, based on reporter assays, as potential targets of miR-106a and the miR-17-92 cluster, respectively. Interestingly, E2F1, which was shown to be a target of miR-17-5p and miR-20a, and is predicted by PicTar to be a target for both miR-106b and miR-93, was significantly downregulated as well. A downregulation of p57 was also observed in WI-38 cells, in agreement with PicTar predictions (Figure 17A and Figure 18). Notably, these proteins have defined functions in the regulation of the cell-cycle, most of them being negative regulators of proliferation. Since the mRNA levels of p57, p21, pRb and p130 did not decrease in WI-38 cells and only marginally in MCF10A cells (Figure 17B), the reduction in their protein levels most likely stems from translational inhibition and not mRNA degradation. In contrast, E2F1 mRNA levels were reduced in both cell lines that express the miR-106b/93/25 polycistron.

Next, the present inventors set out to obtain a global view of the behavior of the predicted targets of the '*p53-repressed miR cluster*'. The expression profiles of these targets in the system described above were analyzed, where primary WI-38 cells were gradually transformed into tumorigenic cells. Interestingly, targets harboring predicted sites in their 3'-UTR for multiple miRs had a significant coherent expression pattern (Figure 17C, EC p-value= 5×10^{-3} , see Table 17, herein below for the target list).

Note - Table 17 lists only mRNAs that were detected by the microarrays published by Milyavsky et al., 2005, Cancer Res 65: 4530-4543. Target predictions are based on PicTar.

Table 17

<i>RefSeq No.</i>	<i>Gene Symbol</i>	<i>Title</i>
NM_000332	SCA1	ataxin 1
NM_000430	PAFAH1B1	platelet-activating factor acetylhydrolase,
NM_000484	APP	amyloid beta A4 protein precursor isoform a
NM_001128	AP1G1	adaptor-related protein complex 1, gamma 1
NM_001241	CCNT2	cyclin T2 isoform a
NM_001400	EDG1	endothelial differentiation, sphingolipid
NM_001432	EREG	epiregulin
NM_001530	HIF1A	hypoxia-inducible factor 1, alpha subunit
NM_001587	OCRL	phosphatidylinositol polyphosphate 5-phosphatase
NM_001731	BTG1	B-cell translocation protein 1
NM_001759	CCND2	cyclin D2
NM_001781	CD69	CD69 antigen (p60, early T-cell activation

NM_001949	E2F3	E2F transcription factor 3
NM_001991	EZH1	enhancer of zeste homolog 1
NM_002222	ITPR1	inositol 1,4,5-triphosphate receptor, type 1
NM_002267	KPNA3	karyopherin alpha 3
NM_002268	KPNA4	karyopherin alpha 4
NM_002401	MAP3K3	mitogen-activated protein kinase kinase kinase 3
NM_002515	NOVA1	neuro-oncological ventral antigen 1 isoform 1
NM_002628	PFN2	profilin 2 isoform b
NM_002655	PLAG1	pleiomorphic adenoma gene 1
NM_002721	PPP6C	protein phosphatase 6, catalytic subunit
NM_002868	RAB5B	RAB5B, member RAS oncogene family
NM_003077	SMARCD2	SWI/SNF-related matrix-associated
NM_003137	SRPK1	SFRS protein kinase 1
NM_003155	STC1	stanniocalcin 1
NM_003483	HMGA2	high mobility group AT-hook 2
NM_003895	SYNJ1	synaptojanin 1 isoform a
NM_003954	MAP3K14	mitogen-activated protein kinase kinase kinase
NM_004050	BCL2L2	BCL2-like 2 protein
NM_004093	EFNB2	ephrin B2
NM_004171	SLC1A2	solute carrier family 1, member 2
NM_004240	TRIP10	thyroid hormone receptor interactor 10
NM_004308	ARHGAP1	Rho GTPase activating protein 1
NM_004444	EPHB4	ephrin receptor EphB4 precursor
NM_004459	FALZ	fetal Alzheimer antigen isoform 2
NM_004505	USP6	ubiquitin specific protease 6
NM_004755	RPS6KA5	ribosomal protein S6 kinase, 90kDa, polypeptide
NM_004768	SFRS11	splicing factor p54
NM_004898	CLOCK	clock
NM_004984	KIF5A	kinesin family member 5A
NM_005230	ELK3	ELK3 protein
NM_005328	HAS2	hyaluronan synthase 2
NM_005458	GPR51	G protein-coupled receptor 51
NM_005502	ABCA1	ATP-binding cassette, sub-family A member 1
NM_005736	ACTR1A	ARP1 actin-related protein 1 homolog A,
NM_006037	HDAC4	histone deacetylase 4
NM_006186	NR4A2	nuclear receptor subfamily 4, group A, member 2
NM_006195	PBX3	pre-B-cell leukemia transcription factor 3
NM_006206	PDGFRA	platelet-derived growth factor receptor alpha
NM_006224	PITPN	phosphatidylinositol transfer protein, alpha
NM_006301	MAP3K12	mitogen-activated protein kinase kinase kinase
NM_006352	ZNF238	zinc finger protein 238 isoform 2
NM_006489	NOVA1	neuro-oncological ventral antigen 1 isoform 2
NM_006526	ZNF217	zinc finger protein 217
NM_006561	CUGBP2	CUG triplet repeat, RNA binding protein 2
NM_006628	ARPP-19	cyclic AMP phosphoprotein, 19 kD
NM_006712	FASTK	Fas-activated serine/threonine kinase isoform 1
NM_006823	PKIA	cAMP-dependent protein kinase inhibitor alpha
NM_006826	YWHAQ	tyrosine 3/tryptophan 5 -monooxygenase
NM_006981	NR4A3	nuclear receptor subfamily 4, group A, member 3
NM_007038	ADAMTS5	a disintegrin and metalloprotease with
NM_007375	TARDBP	TAR DNA binding protein
NM_012081	ELL2	elongation factor, RNA polymerase II, 2

NM_012082	ZFPM2	zinc finger protein, multitype 2
NM_012090	MACF1	microfilament and actin filament cross-linker
NM_012199	EIF2C1	eukaryotic translation initiation factor 2C, 1
NM_012257	HBP1	HMG-box transcription factor 1
NM_012325	MAPRE1	microtubule-associated protein, RP/EB family,
NM_013283	MAT2B	methionine adenosyltransferase II, beta isoform
NM_014112	TRPS1	zinc finger transcription factor TRPS1
NM_014283	C1orf9	chromosome 1 open reading frame 9
NM_015678	NBEA	neurobeachin
NM_015716	MINK	misshapen/NIK-related kinase isoform 1
NM_016227	C1orf9	membrane protein CH1
NM_016231	NLK	nemo like kinase
NM_016308	UMP-CMPK	UMP-CMP kinase
NM_016441	CRIM1	cysteine-rich motor neuron 1
NM_018700	TRIM36	tripartite motif protein 36
NM_021145	DMTF1	cyclin D binding myb-like transcription factor
NM_021813	BACH2	BTB and CNC homology 1, basic leucine zipper
NM_022133	SNX16	sorting nexin 16 isoform a
NM_022898	BCL11B	B-cell CLL/lymphoma 11B isoform 2
NM_032998	DEDD	death effector domain-containing protein
NM_033015	FASTK	Fas-activated serine/threonine kinase isoform 4
NM_033044	MACF1	microfilament and actin filament cross-linker
NM_053024	PFN2	profilin 2 isoform a
NM_053056	CCND1	cyclin D1
NM_058241	CCNT2	cyclin T2 isoform b
NM_138576	BCL11B	B-cell CLL/lymphoma 11B isoform 1
NM_152836	SNX16	sorting nexin 16 isoform a
NM_152837	SNX16	sorting nexin 16 isoform b
NM_153827	MINK	misshapen/NIK-related kinase isoform 3
NM_170663	MINK	misshapen/NIK-related kinase isoform 2
NM_173171	NR4A2	nuclear receptor subfamily 4, group A, member 2
NM_173172	NR4A2	nuclear receptor subfamily 4, group A, member 2
NM_173173	NR4A2	nuclear receptor subfamily 4, group A, member 2
NM_173198	NR4A3	nuclear receptor subfamily 4, group A, member 3
NM_173200	NR4A3	nuclear receptor subfamily 4, group A, member 3
NM_181054	HIF1A	hypoxia-inducible factor 1, alpha subunit
NM_181839	PKIA	cAMP-dependent protein kinase inhibitor alpha
NM_182641	FALZ	fetal Alzheimer antigen isoform 1
NM_182796	MAT2B	methionine adenosyltransferase II, beta isoform
NM_199324	HSHIN1	HIV-1 induced protein HIN-1 isoform 1
NM_201413	APP	amyloid beta A4 protein precursor isoform b
NM_201414	APP	amyloid beta A4 protein precursor isoform c
NM_203351	MAP3K3	mitogen-activated protein kinase kinase kinase 3
NM_205768	ZNF238	zinc finger protein 238 isoform 1
NM_212467	CAPN3	calpain 3 isoform h

The expression of this target set was decreased when cells gained the accelerated proliferation phenotype (designated as "Fast Growing"), i.e. most of these targets showed a clear anti-proliferative expression pattern. Promoter analysis of these predicted target set revealed that one of the most highly enriched motifs was E2F (p-value=2.2x10⁻¹³). Hence,

genes heavily targeted by the p53-repressed miRs are characterized by anti-proliferative behavior. This may suggest that the feed-forward loop that consists of E2F and miR-106b/93/25 may be de-regulated during cancer progression, by downregulation of these anti-proliferative targets both transcriptionally and post-transcriptionally.

5 Having shown the molecular effects of the overexpression of miR-106b/93/25, the present inventors tested whether proliferation-related parameters such as growth rate, colony formation efficiency and replicative senescence are affected by these miRs. As these miRs are significantly repressed by p53 during senescence, and considering the fact that they target several anti-proliferation regulators, it was predicted that their
10 overexpression, similarly to p53 inactivation, would accelerate growth rate and delay senescence. Indeed, as depicted in Figure 19A-D, the miR-106b/93/25 overexpressing WI-38 cells demonstrated a moderate acceleration in proliferation rate and an increased fraction of S-phase cells (24 % compared to 18 %). Strikingly, these cells displayed a pronounced increase in the efficiency of young cells to form colonies when seeded at low
15 density and reduced SA- β -Gal staining at late passages, indicating a delay of replicative senescence. These observed phenotypes, which mimic the effect of p53 inactivation in primary cells (Figures 10A-F and Figures 13A-D), suggest that the transcriptional repression of miR-106b/93/25 and their paralogs mediates part of the anti-proliferative effects of p53.

20 Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

25 All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference
30 is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the
5 appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of
10 any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A method of identifying components of a biological pathway, the method comprising selecting a transcription factor and a microRNA pair which regulate a common gene, said transcription factor and said microRNA being the components of the biological pathway.
2. The method of claim 1, wherein said transcription factor and said microRNA pair are listed in Tables 5-8.
3. The method of claim 1, wherein a gene encoding said microRNA comprises a binding site for said transcription factor and/or a gene encoding said transcription factor comprises a binding site for said microRNA.
4. The method of claim 3, wherein said transcription factor and said microRNA pair are listed in Table 9-11.
5. The method of claim 3, wherein said transcription factor and said microRNA pair are listed in Figure 4.
6. The method of claim 1, wherein said transcription factor regulates a transcription of an additional transcription factor, said microRNA comprising a binding site for said additional transcription factor.
7. The method of claim 6, wherein said transcription factor and said microRNA are listed in Tables 12-14.
8. A method of treating a hyperproliferative disease in a subject, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide agent capable of down-regulating at least one microRNA selected from the group consisting miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2*, hsa-miR-19b-1* miR-15b, miR-16, hsa-miR-92a-2*, and hsa-miR-92a-1* into the subject, thereby treating the hyperproliferative disease.

9. The method of claim 8, wherein the hyperproliferative disease is cancer.

10. A method of treating a degenerative disease in a subject, the method comprising administering to the subject a therapeutically effective amount of at least one microRNA selected from the group consisting of miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2*, hsa-miR-19b-1* miR-15b, miR-16, hsa-miR-92a-2*, and hsa-miR-92a-1* into the subject, thereby treating the degenerative disease.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active agent at least one microRNA selected from the group consisting of miR-106b, miR-93, miR-25, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92a-1, miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, miR-15b and miR-16.

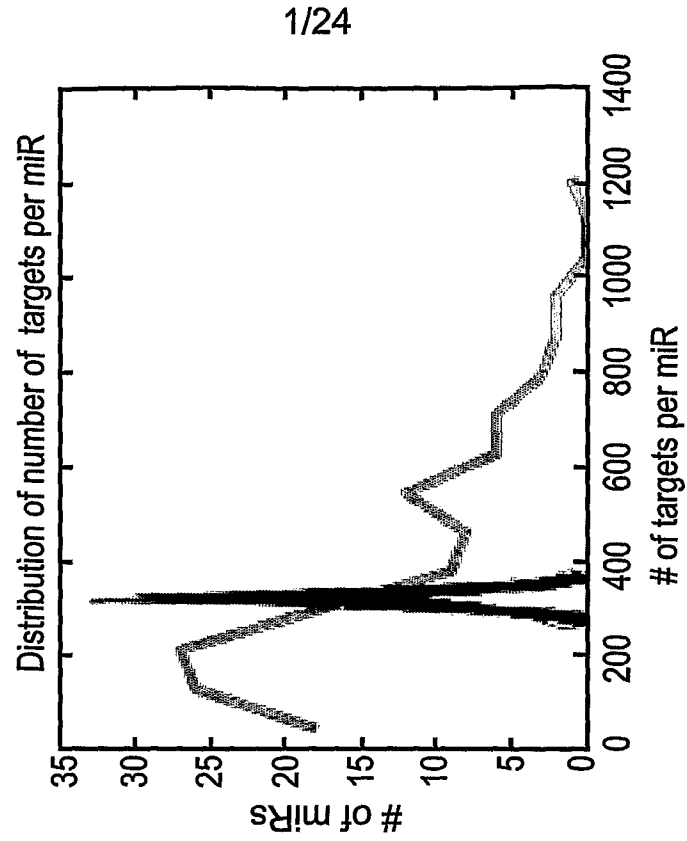


Fig. 1B

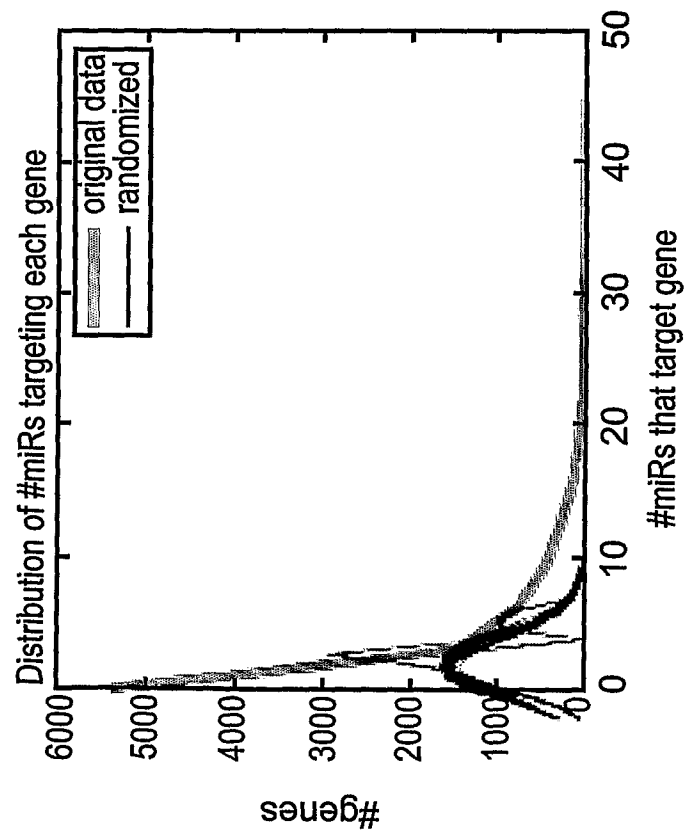


Fig. 1A

2/24

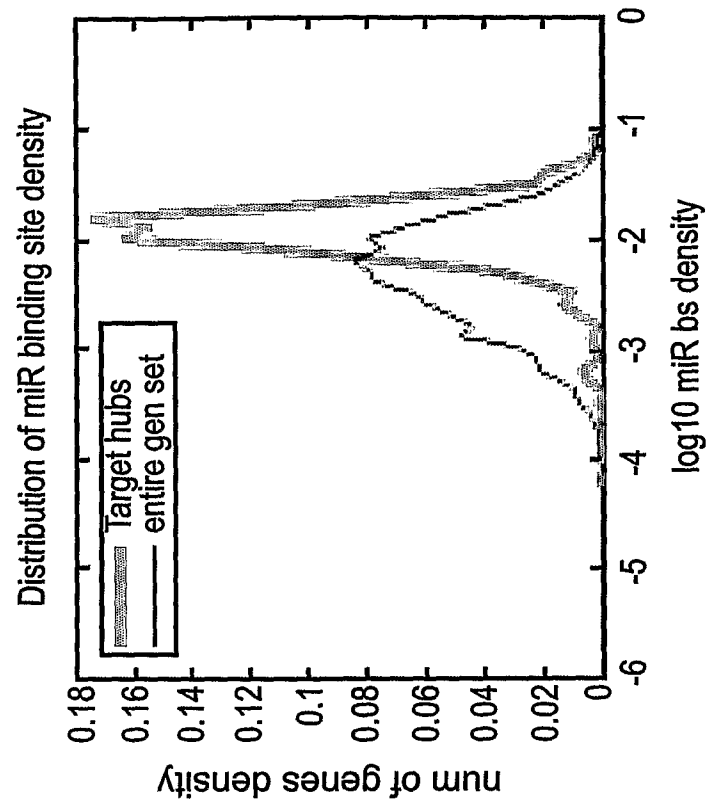


Fig. 2B

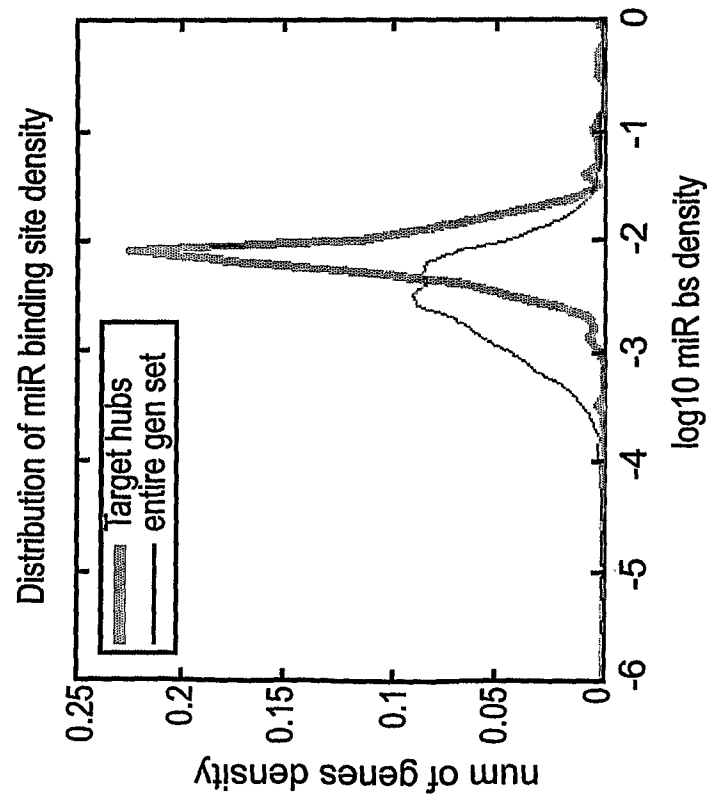


Fig. 2A

3/24

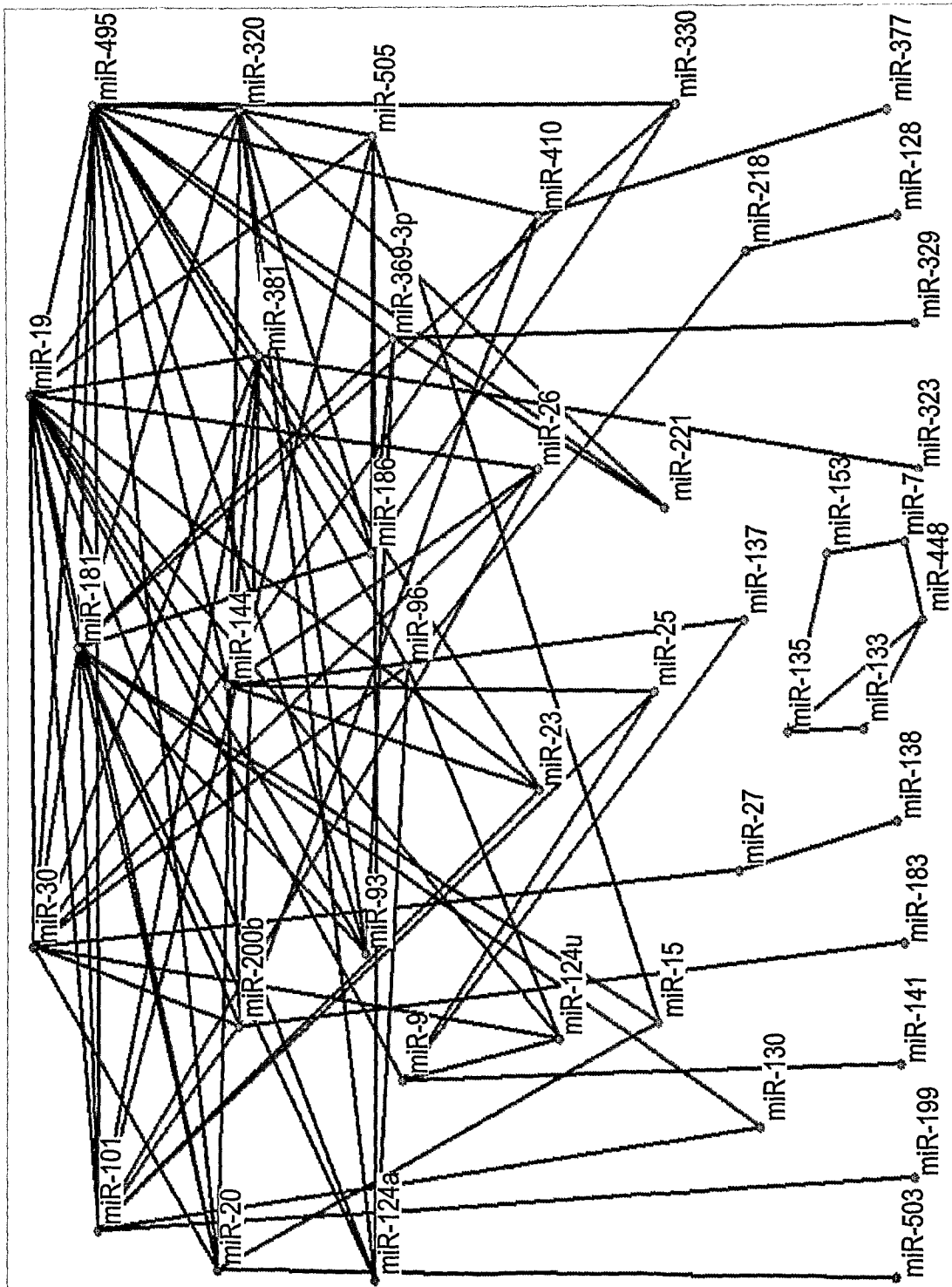


Fig. 3A

4/24

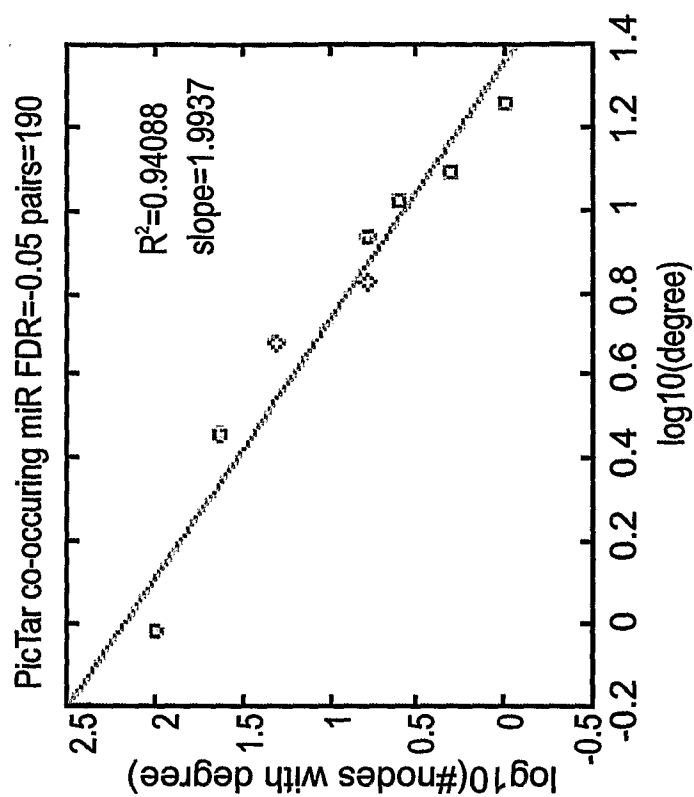


Fig. 3C

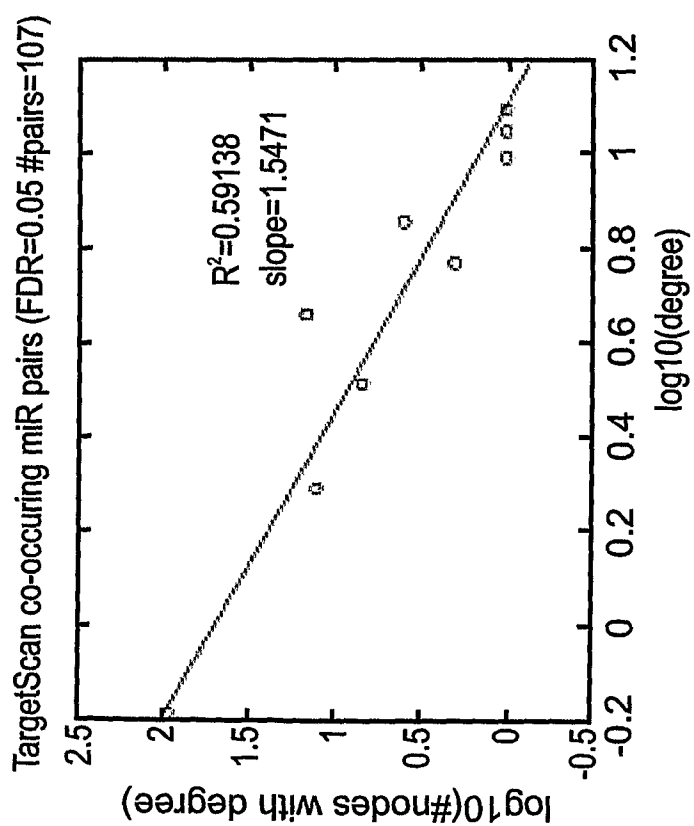


Fig. 3B

5/24

Fig. 4

Motif	Diagram	Number of appearances		p-value	Z-score	Number of genes	example
Significant pair		TargetScan	104	$6 \cdot 10^{-5} \cdot 5 \cdot 10^{-4}$ ($<10^{-3}$)	2.49- 10.15**	1017	miR-1 & VSCREBPICIUN_01
		PicTar 5kb	497	$1 \cdot 10^{-7} \cdot 2 \cdot 10^{-3}$ ($<10^{-5}$)	2.55- 21.42**	1959	
		PicTar 10kb	916	$2 \cdot 10^{-6} \cdot 5 \cdot 10^{-3}$ ($<6 \cdot 10^{-3}$)	2.13- 13.49**	3336	
Feed Forward loop (FFL) TF → miR		TargetScan	10	0.0255	2.36	182	VSIRF2_01 → miR-10
		PicTar 5kb	45	$<10^{-4}$	5.3	493	
		PicTar 10kb	75	$<10^{-4}$	5.58	861	
FFL miR → TF		TargetScan	5	0.14	1.39	94	miR-14S → VSFOX_Q2
		PicTar 5kb	42	$<10^{-4}$	6.03	275	
		PicTar 10kb	48	0.0038	2.93	455	
Composite loop miR ↔ TF		TargetScan	0	-	-	-	Cluster miR-25, miR-93, miR-106b & VSE2F: E2F → miR-93 & All three → E2F
		PicTar 5kb	6	$4 \cdot 10^{-4}$	5.27	76	
		PicTar 10kb	7	0.0024	4.02	116	
Indirect FFL		TargetScan	30	0.0013	3.32	485	VSSRF_Q6 → VSKROX_Q6 and VSNGFIC_D1 → miR- 19b
		PicTar 5kb	95	$<10^{-4}$	4.55	855	
		PicTar 10kb	201	$<10^{-4}$	4.28	1635	

6/24

Normalized distribution of TF-miR tissue expression correlations



Fig. 5A

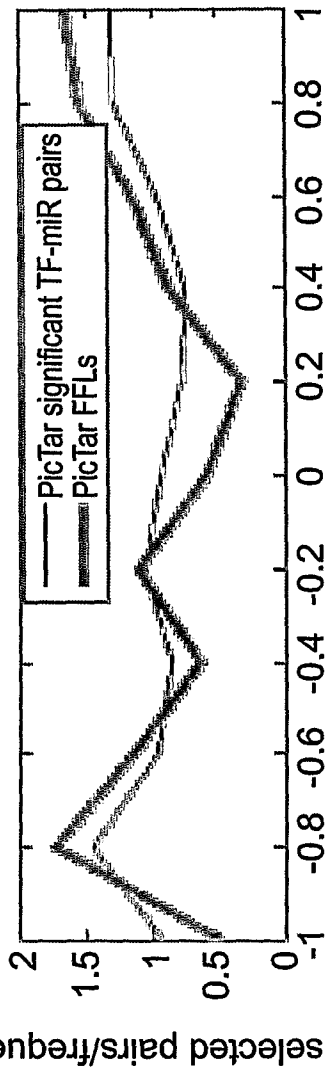


Fig. 5B

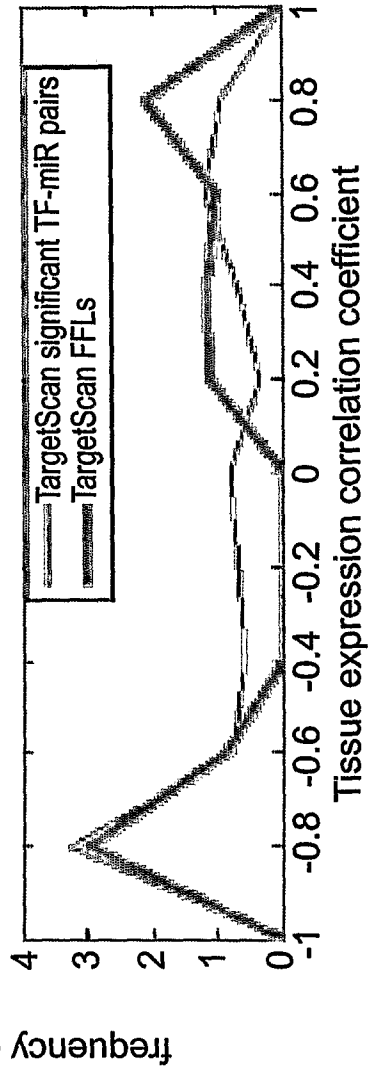


Fig. 5C

7/24

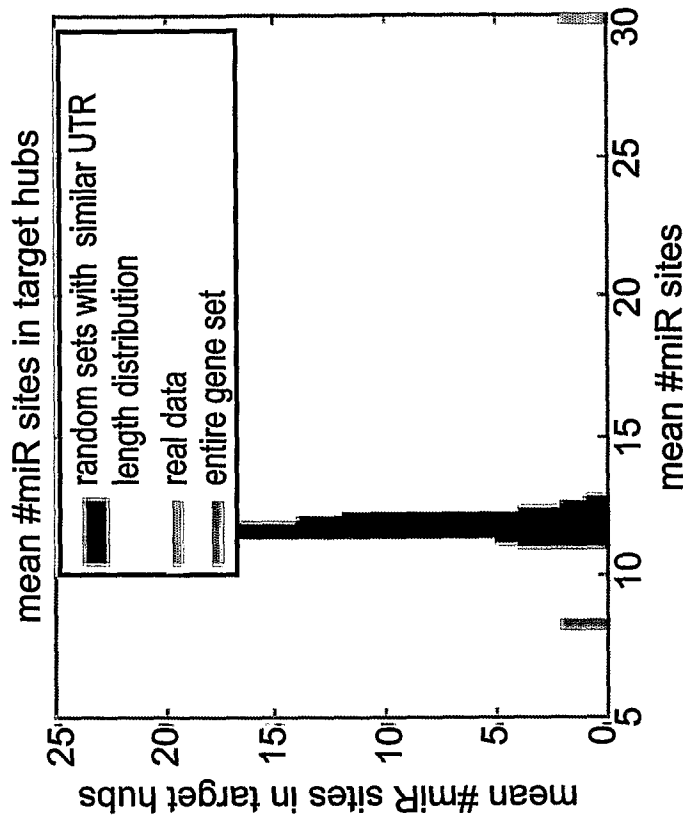


Fig. 6B

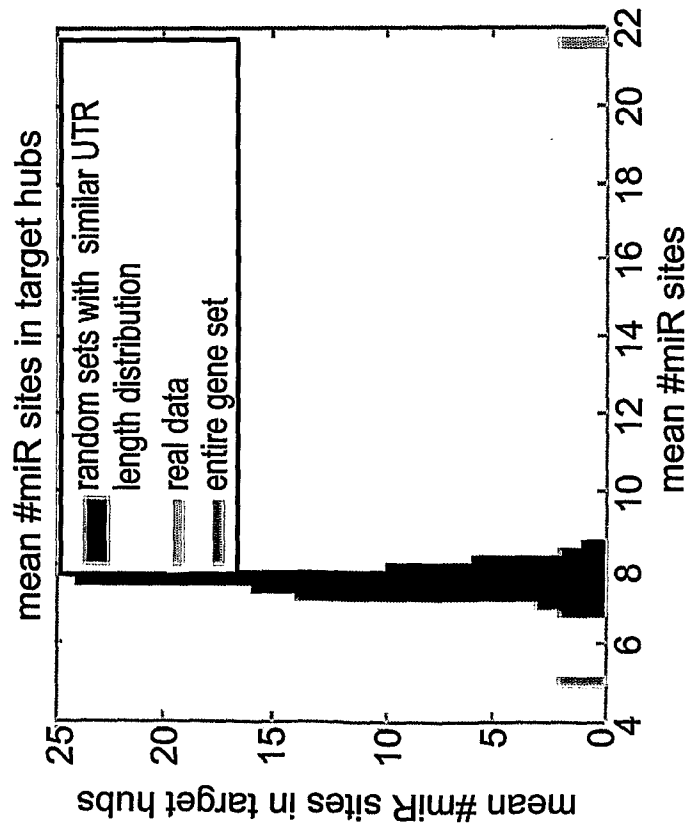


Fig. 6A

8/24

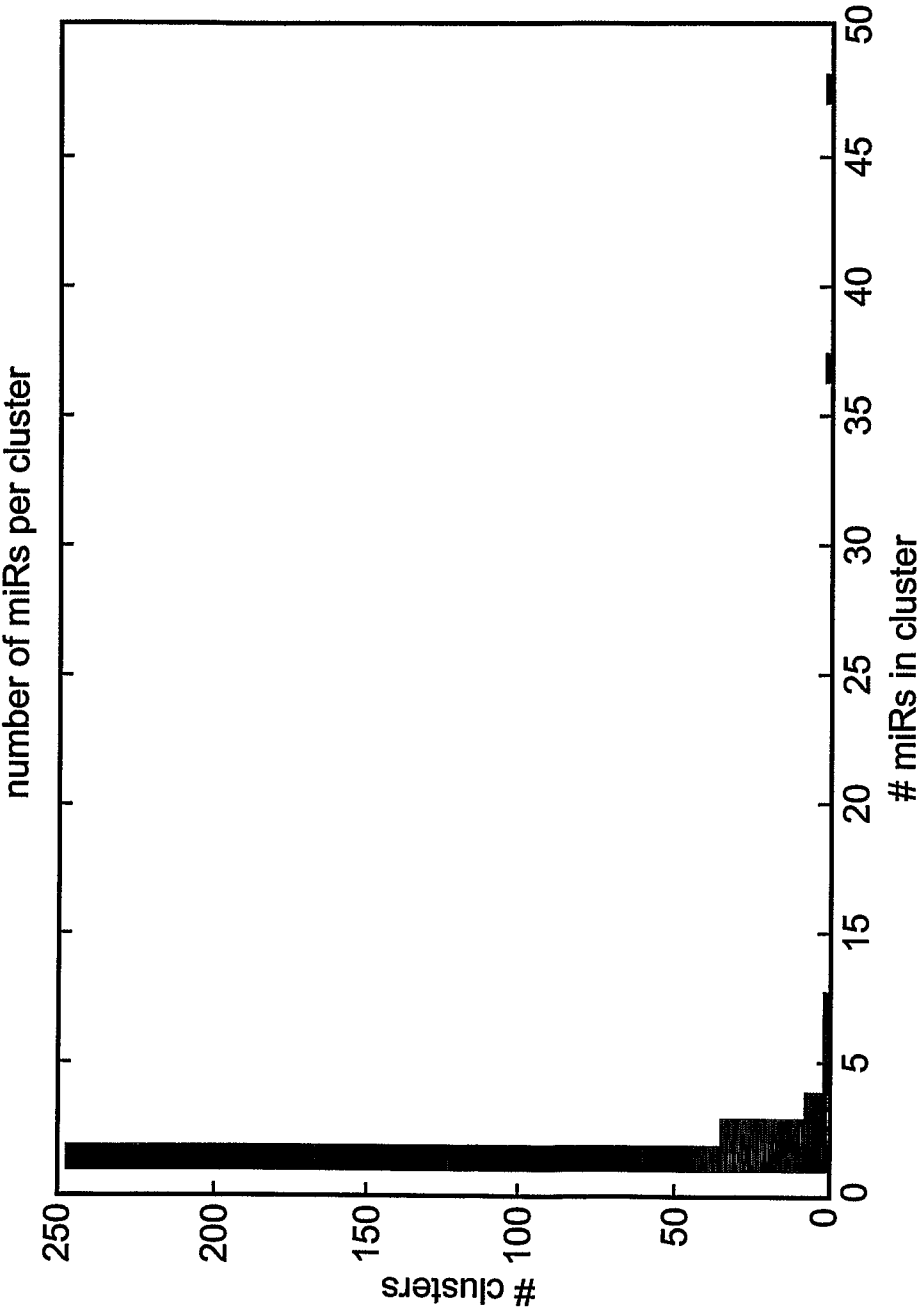
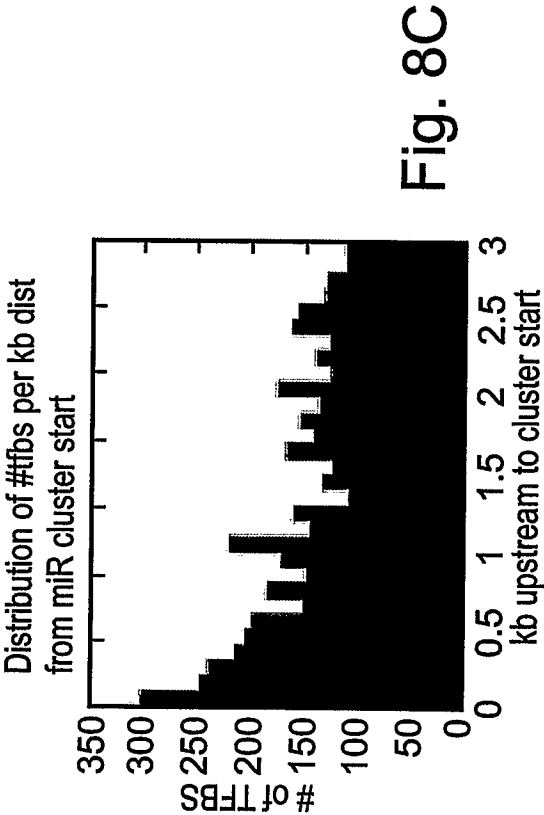
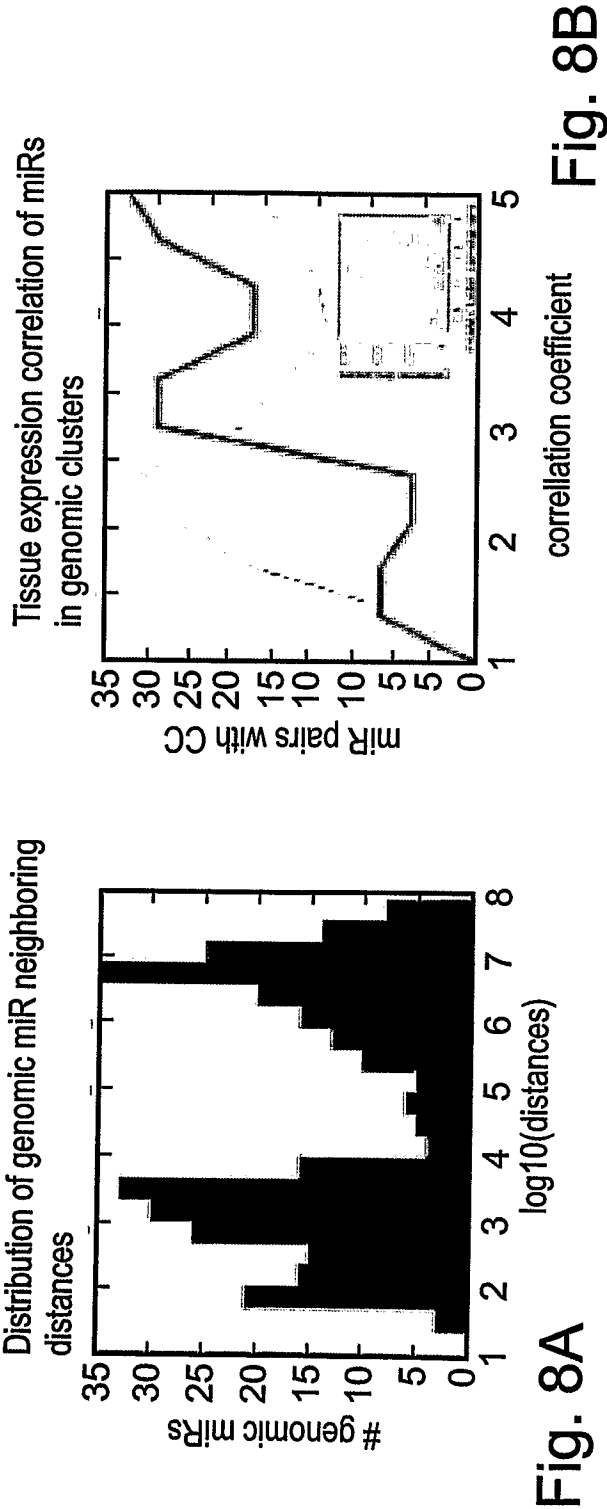


Fig. 7

9/24



10/24

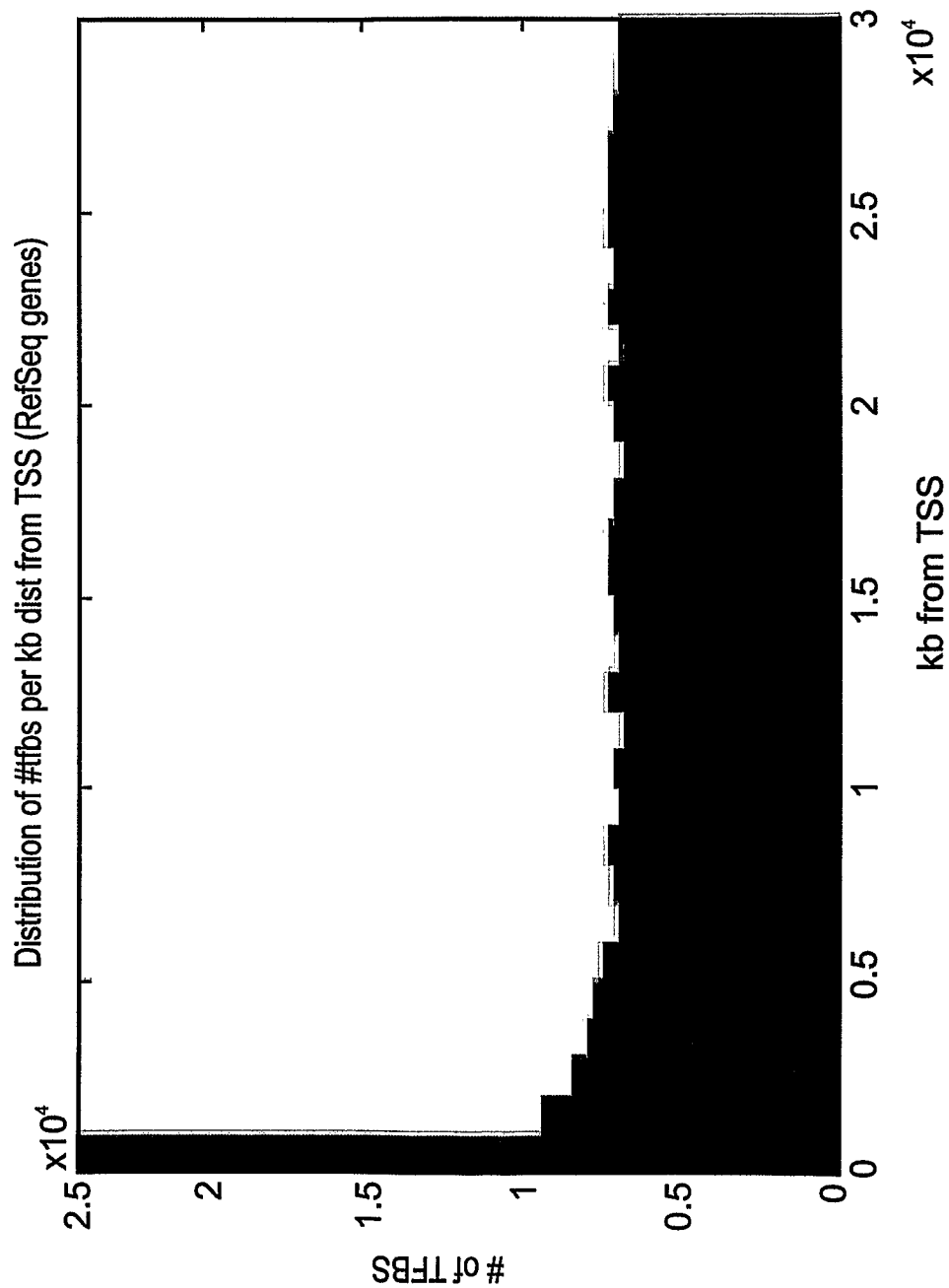


Fig. 9

11/24

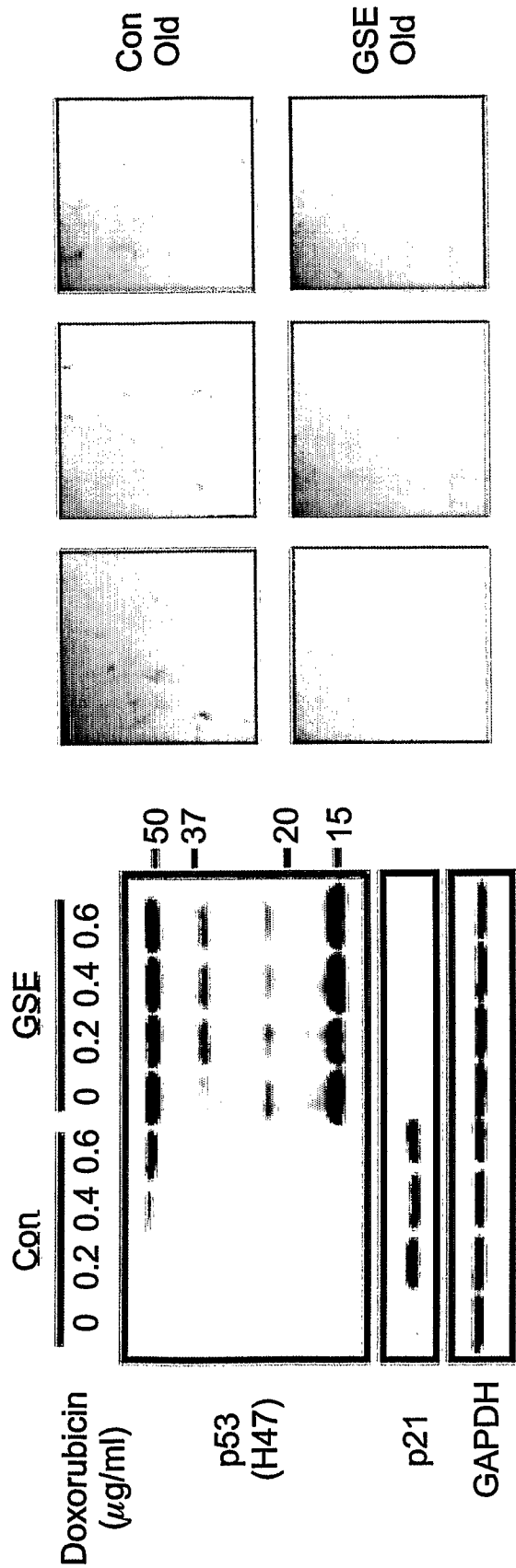
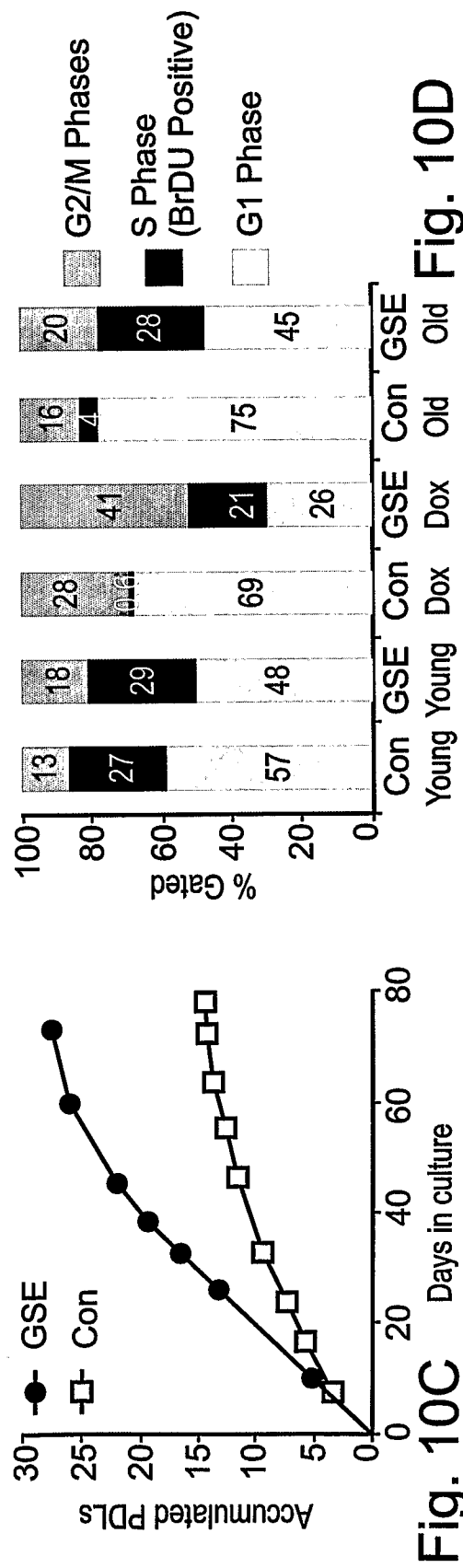
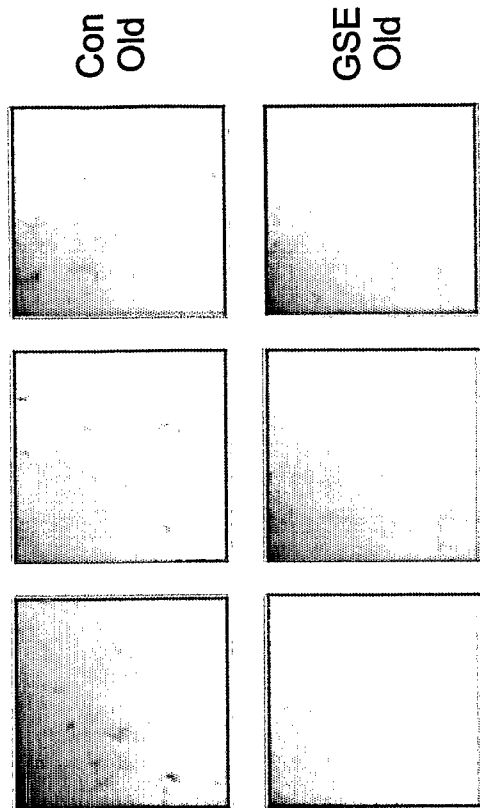


Fig. 10B



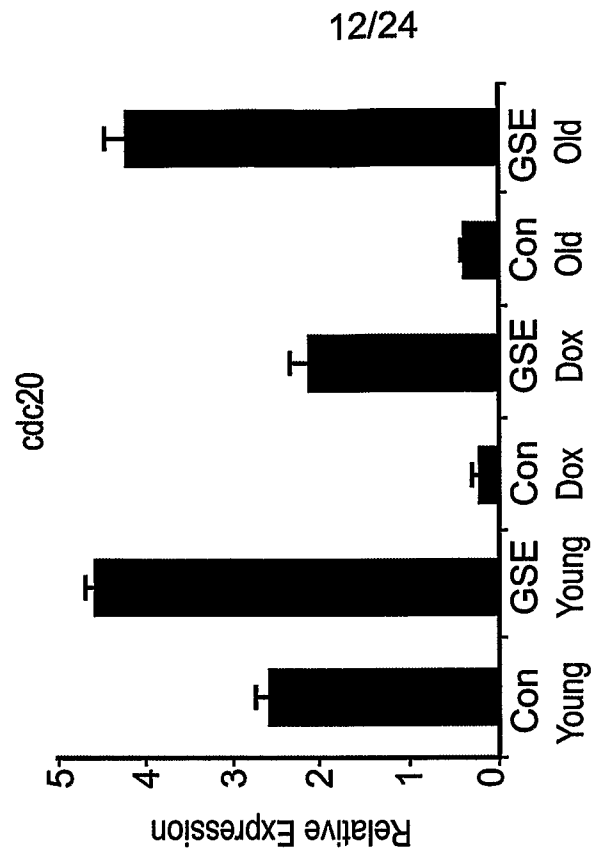


Fig. 10F

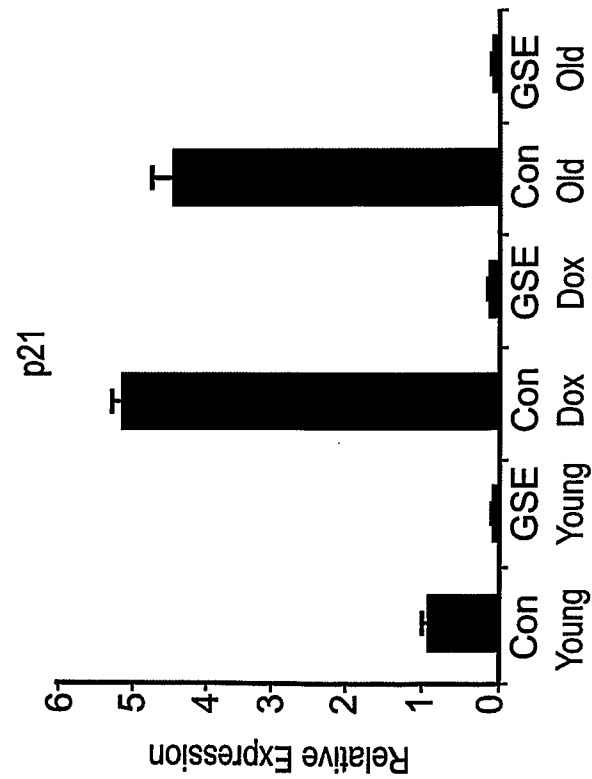
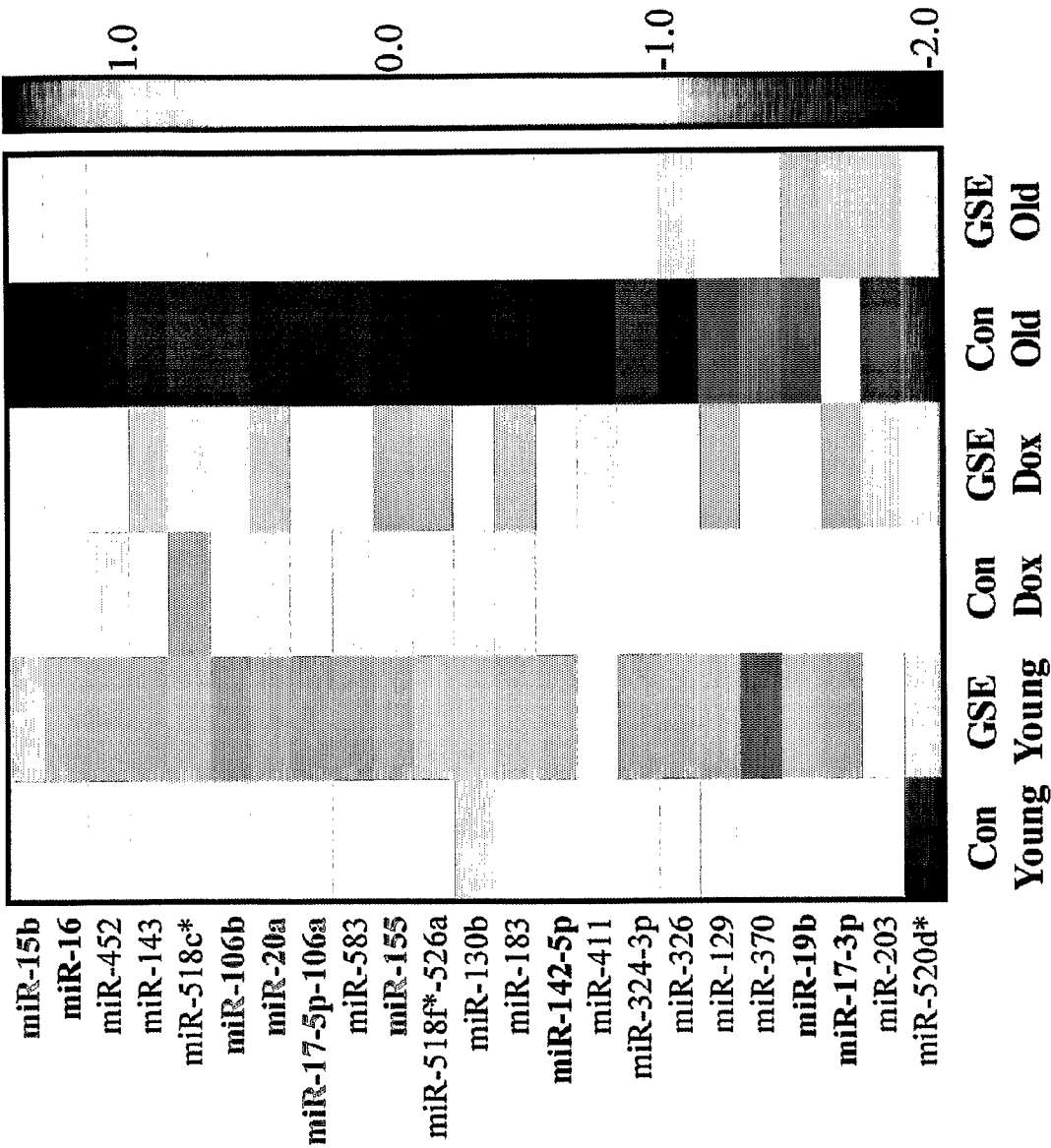


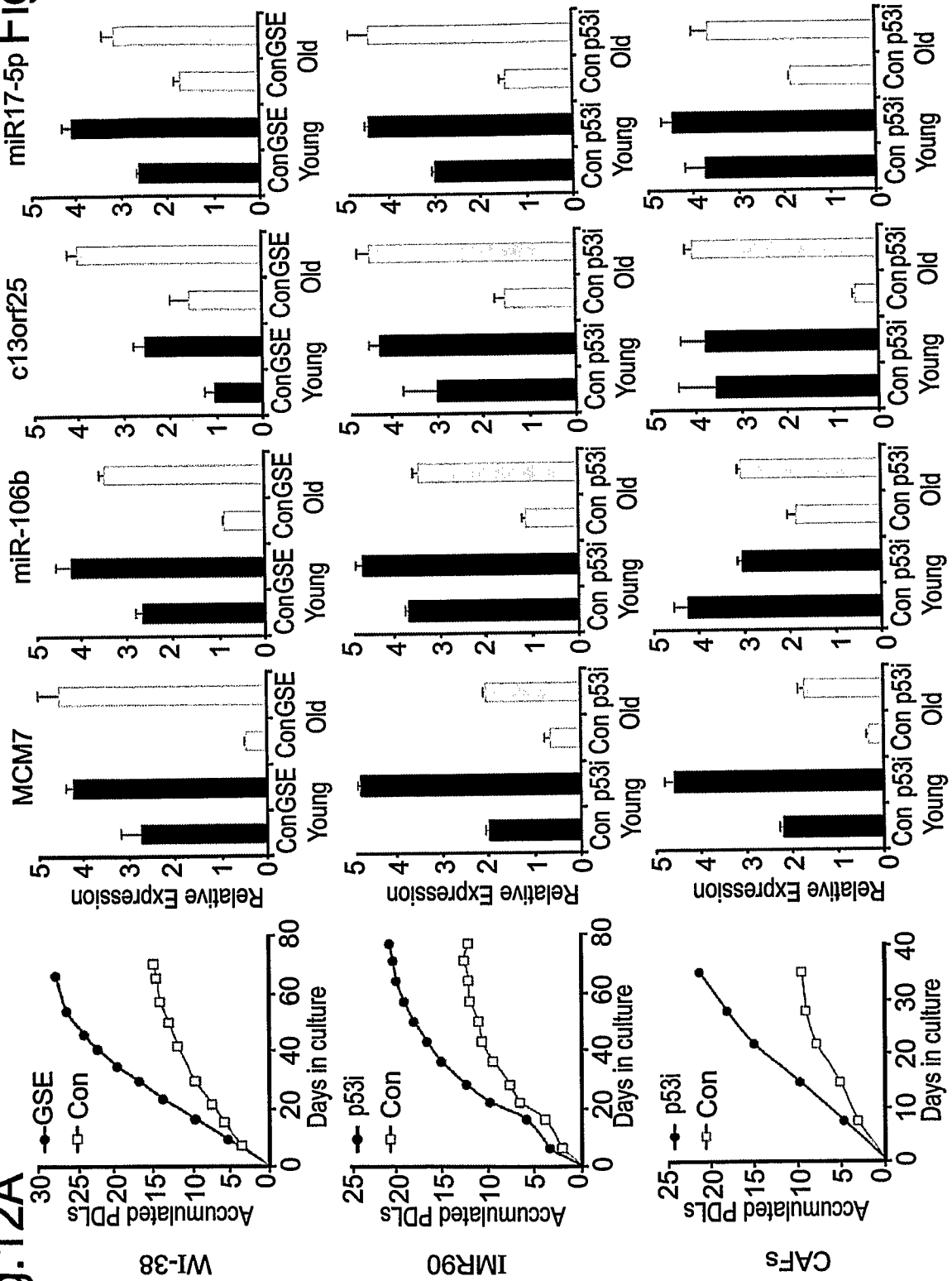
Fig. 10E

p53-repressed miR cluster



14/24

Fig.12A Fig.12B



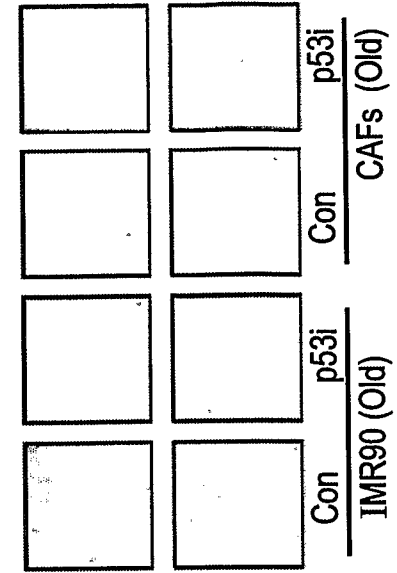


Fig. 13C

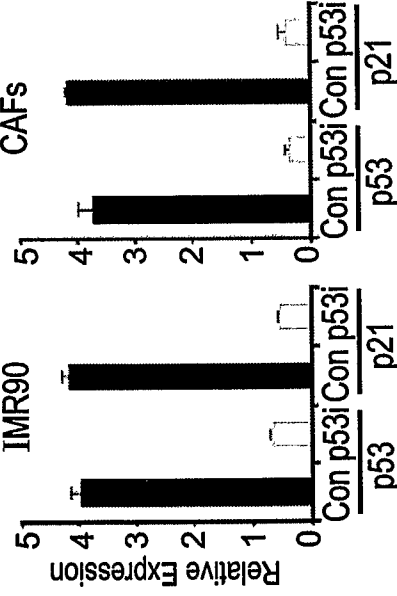


Fig. 13B

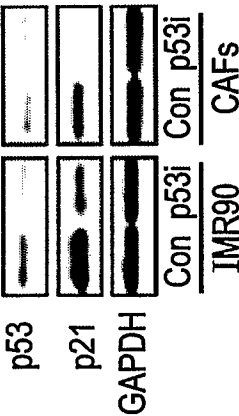


Fig. 13A

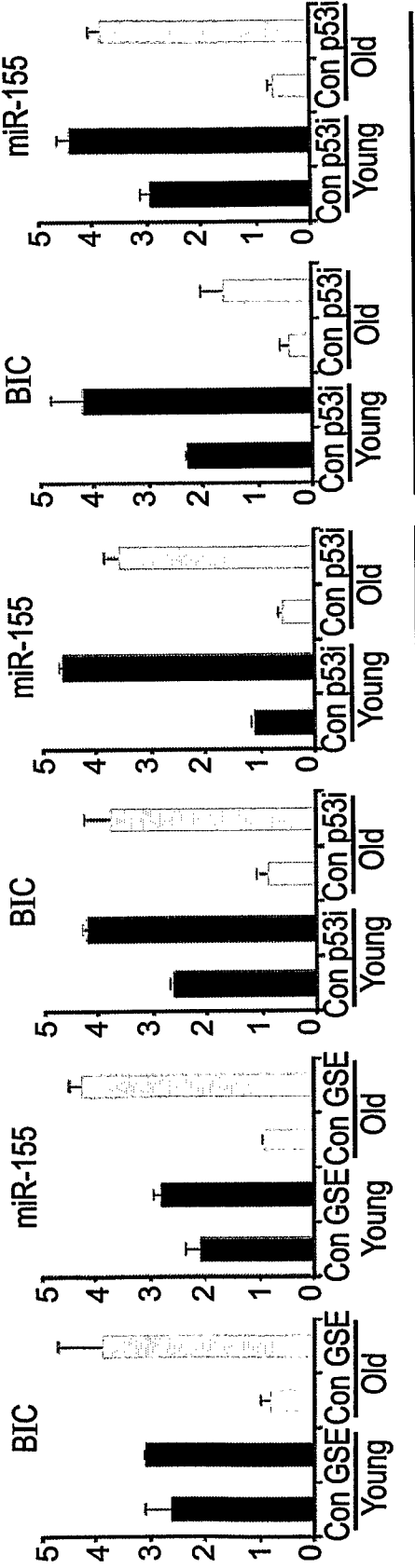
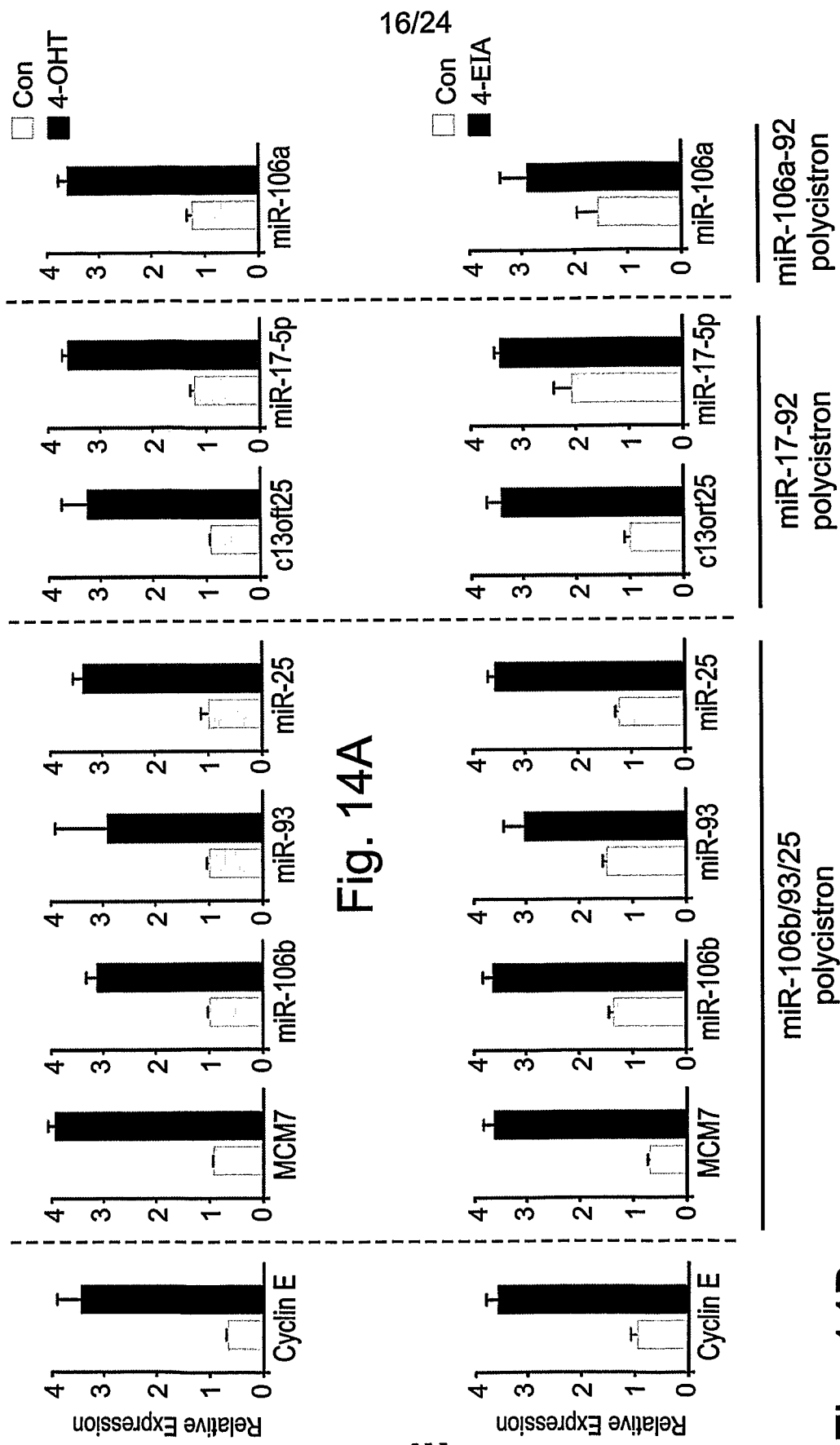


Fig. 13D



17/24

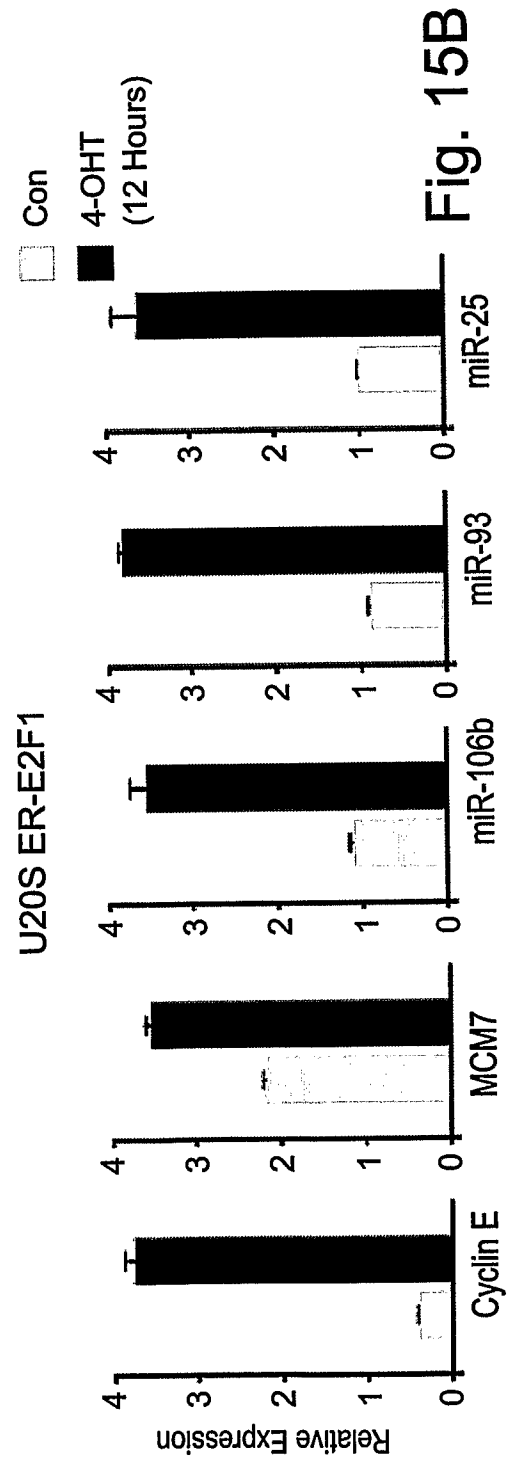
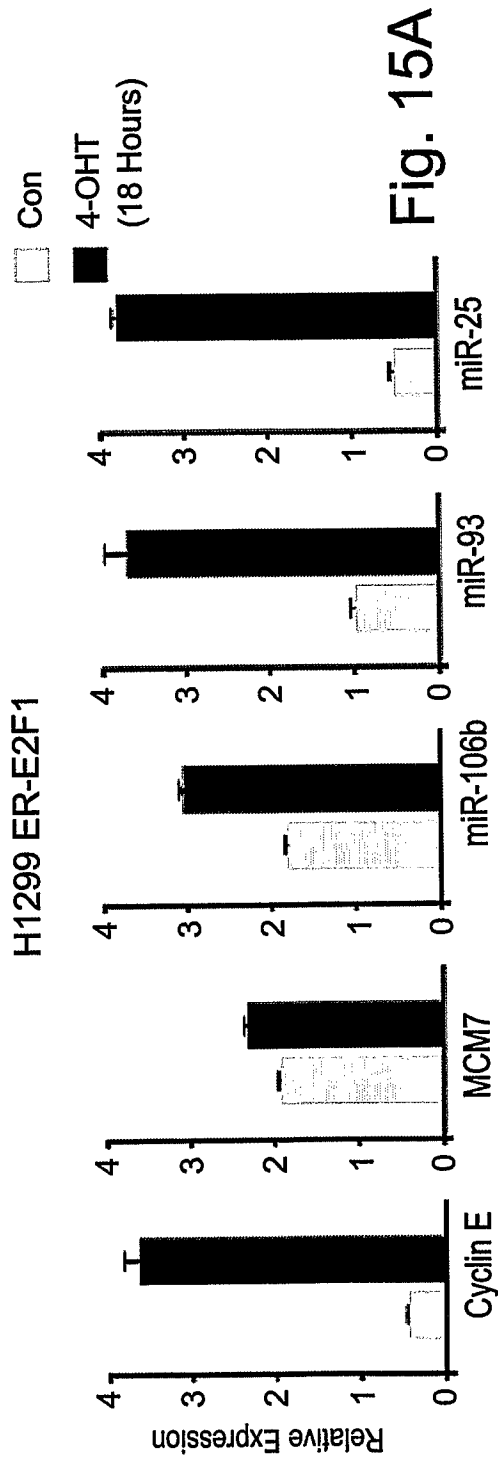


Fig. 16A

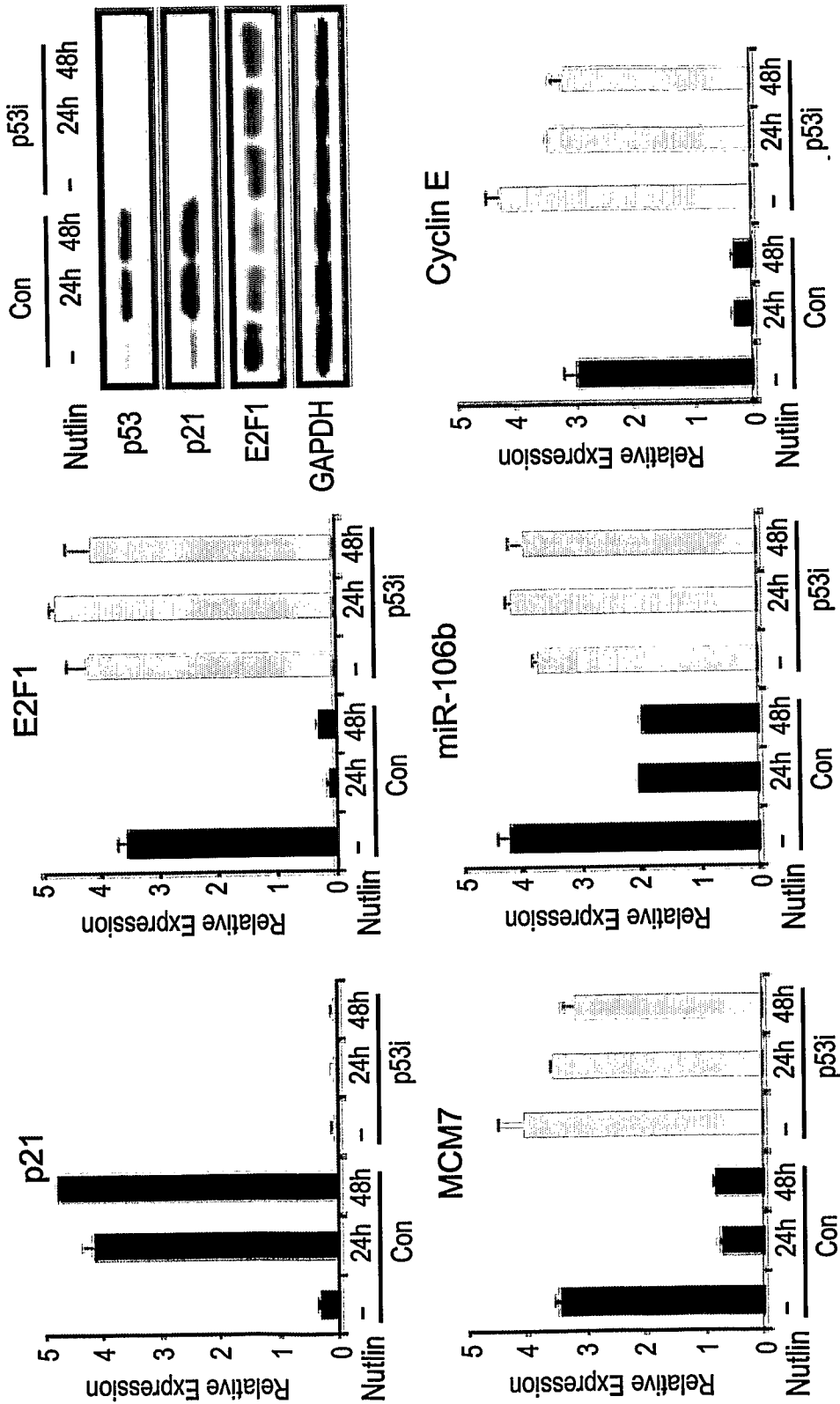


Fig. 16B

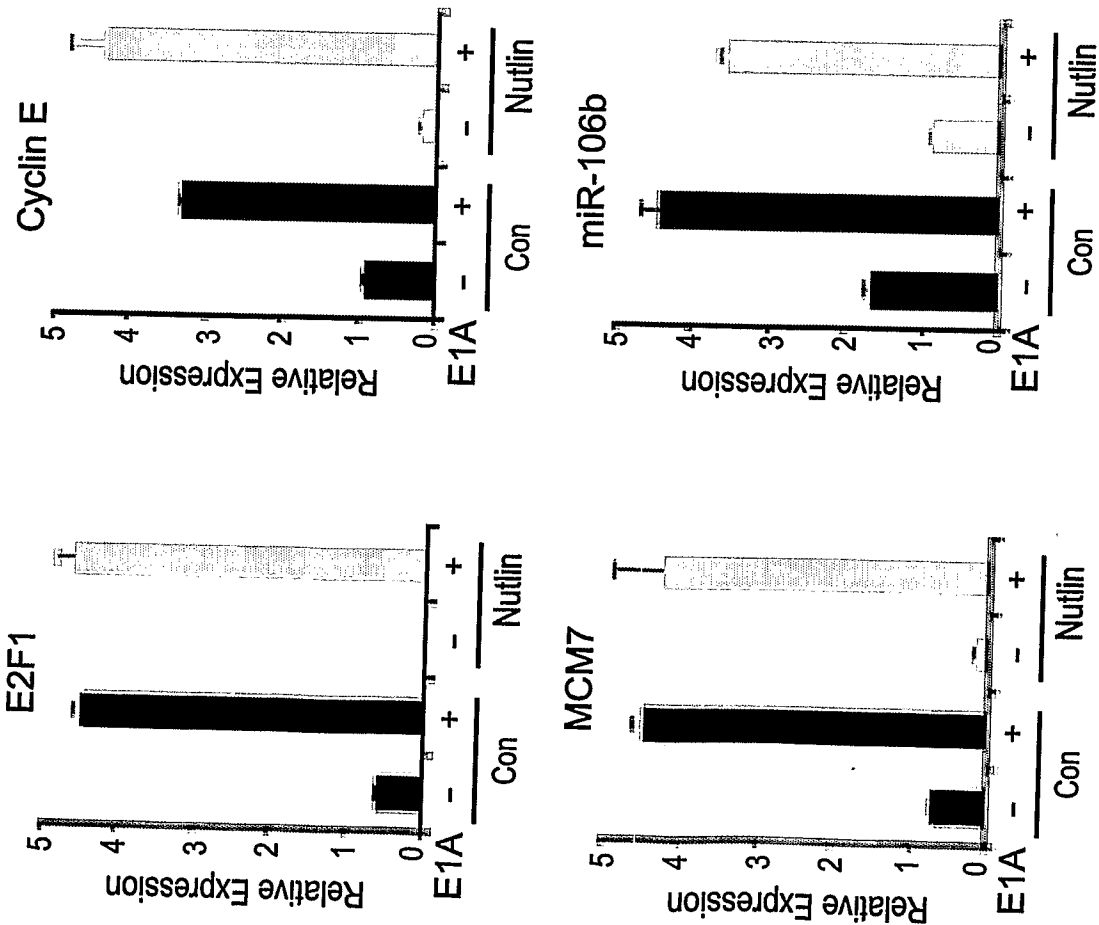


Fig. 16C

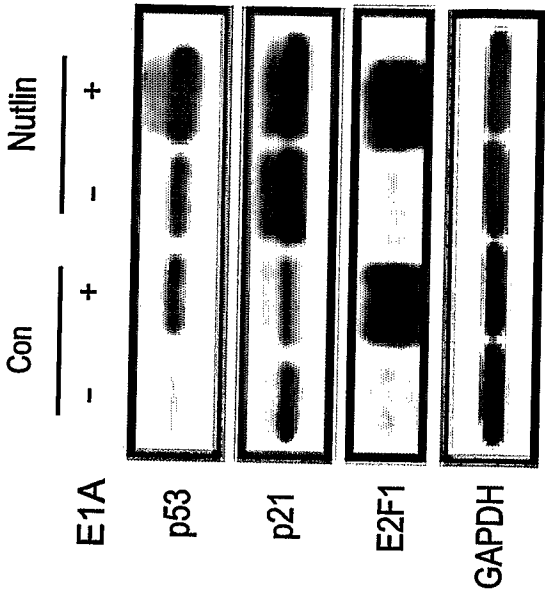


Fig. 16D

20/24

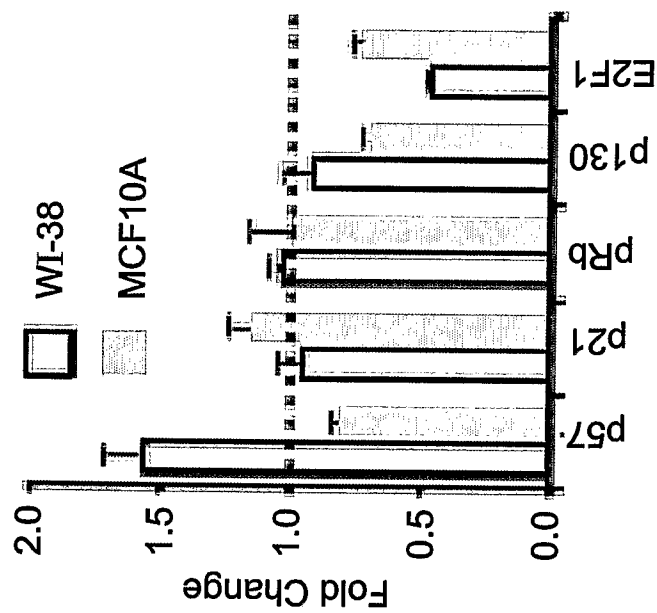


Fig. 17B

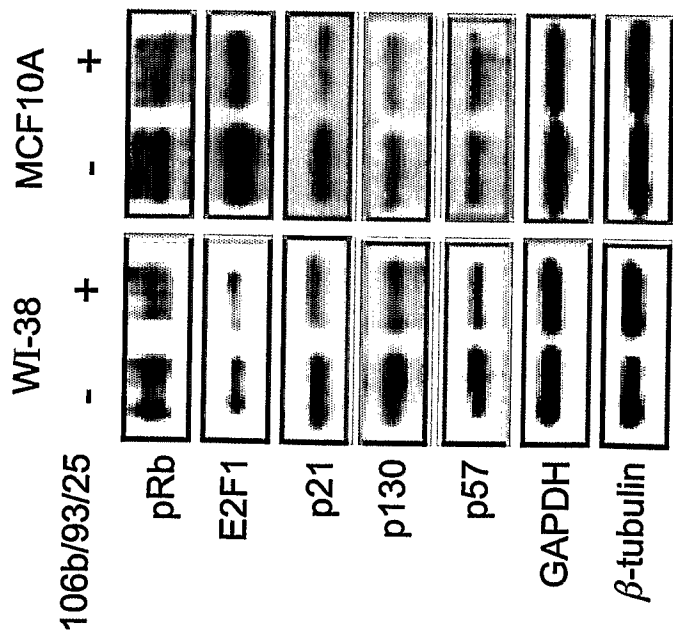


Fig. 17A

Fig. 17D

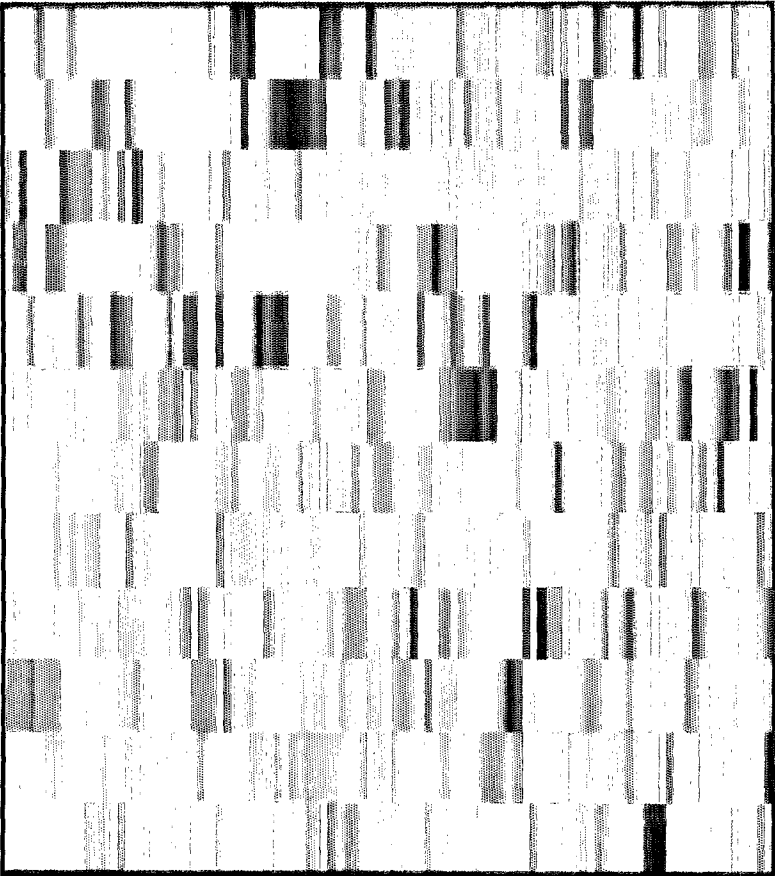
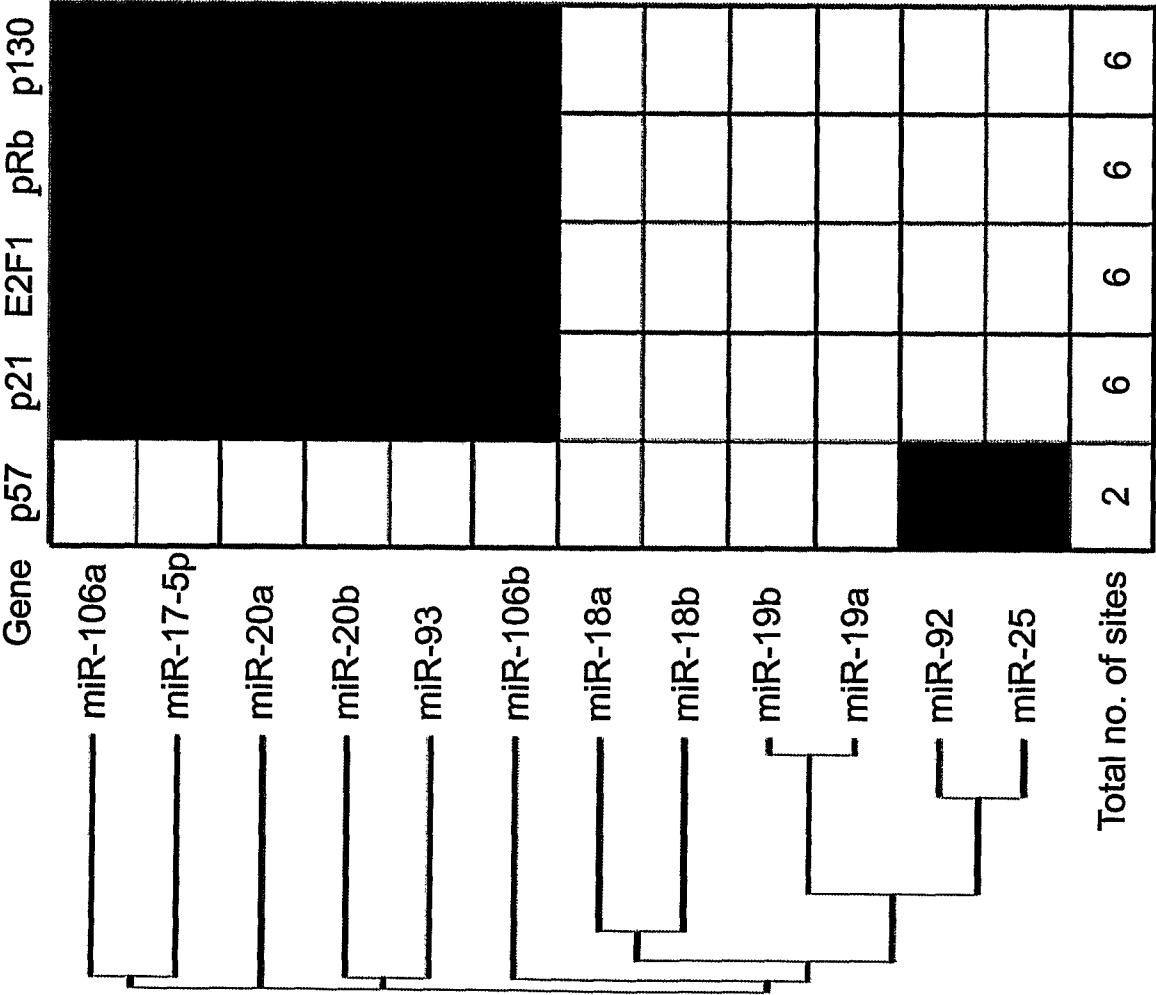


Fig. 17C
mRNA targets of the "p53-repressed miR cluster"

passage	21	23	29	29	28	28	52	69	97	120	96	96	96	96
GSE56	-	+	-	+	-	-	-	-	-	-	-	+	+	+
hTERT	-	-	-	-	+	+	+	+	+	+	+	+	+	+
H-RasV12	-	-	-	-	-	-	-	-	-	-	+	+	-	-
p16 cyp	+	+	+	+	+	+	+	+	-	-	-	-	-	-
	Slow Growing								Fast Growing					

Fig. 18



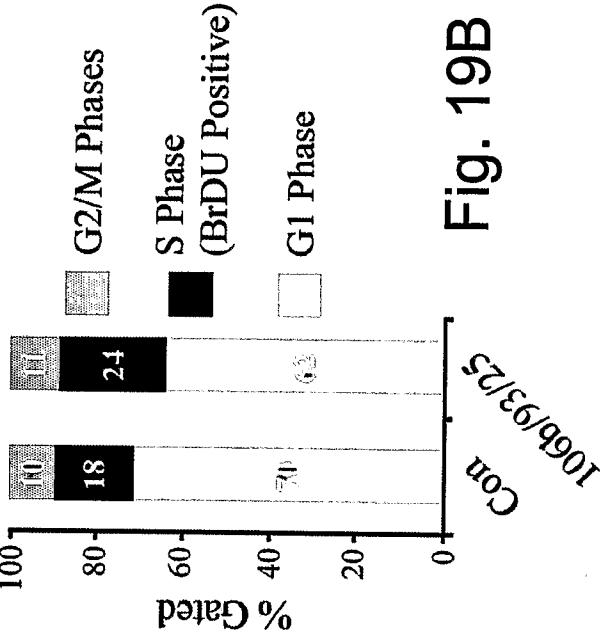


Fig. 19B

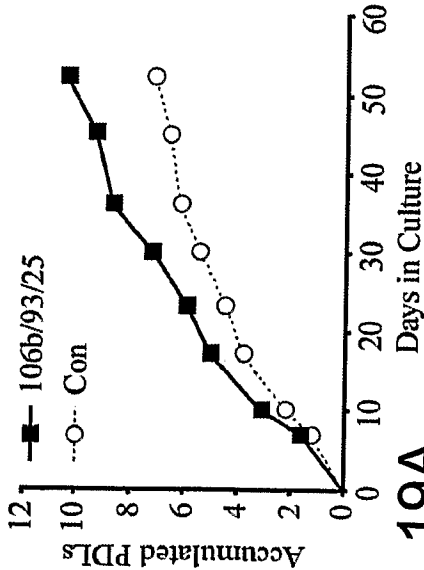


Fig. 19A

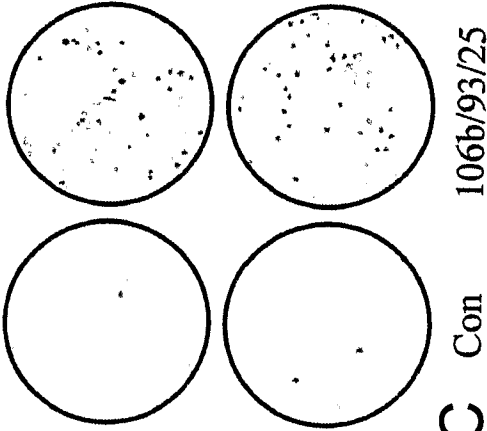
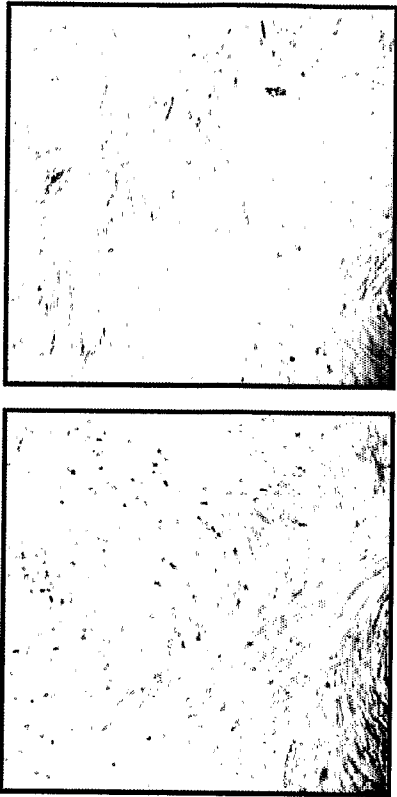


Fig. 19C



Con

106b/93/25

Fig. 19D

24/24

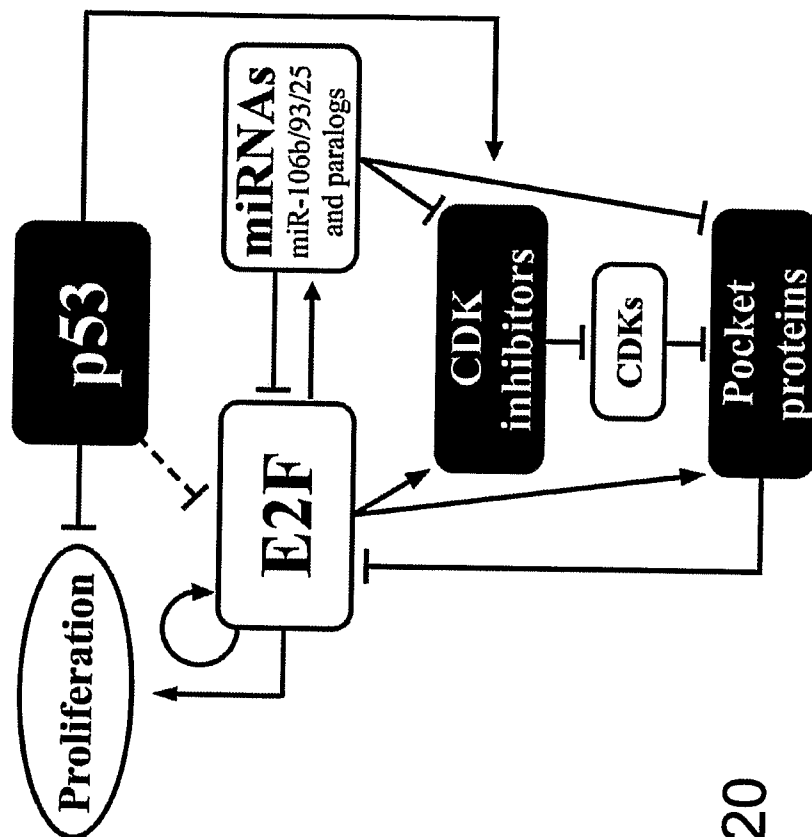


Fig. 20