Send Orders for Reprints to reprints@benthamscience.ae

Current Genomics, 2015, *16*, 349-358

MicroRNAs in Lymphoma: Regulatory Role and Biomarker Potential

Marta Fernandez-Mercado[a], Lorea Manterola[a] and Charles H. Lawrie[a,b,c,*]

[a]*Oncology area, Biodonostia Research Institute, San Sebastián, Spain;* [b]*Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, UK;* [c]*IKERBASQUE, Basque Foundation for Science, Bilbao, Spain*

C.H. Lawrie

Abstract: Although it is now evident that microRNAs (miRNAs) play a critical regulatory role in many, if not all, pathological and physiological processes, remarkably they have only formally been recognized for less than fifteen years. These endogenously produced short non-coding RNAs have created a new paradigm of gene control and have utility as both novel biomarkers of cancer and as potential therapeutics. In this review we consider the role of miRNAs in lymphoid biology both under physiological (i.e. lymphopoiesis) and malignant (i.e. lymphomagenesis) conditions. In addition to the functional significance of aberrant miRNA expression in lymphomas we discuss their use as novel biomarkers, both as a *in situ* tumour biomarker and as a non-invasive surrogate for the tumour by testing miRNAs in the blood of patients. Finally we consider the use of these molecules as potential therapeutic agents for lymphoma (and other cancer) patients and discuss some of the hurdles yet to be overcome in order to translate this potential into clinical practice.

Keywords: Biomarker, Hematological malignancies, Lymphoid, Lymphoma, microRNA, ncRNA.

1. INTRODUCTION

According to the central dogma of molecular biology, biological information flows in one direction from DNA to RNA to protein [1]. The logical consequence of this dogma is that non-coding RNA (ncRNA) has no intrinsic value, however over 90% of transcriptional output in eukaryotes are non-coding [2]. Therefore it is perhaps unsurprising that microRNAs (miRNAs) were unknown to science up until just over 20 years ago, and not formally recognized until 2001 [3]. Now we realize that miRNAs play key regulatory roles in nearly every aspect of biology including cell differentiation, developmental timing, cell proliferation, apoptosis, organ development, metabolism, and hematopoiesis [4]. Approximately, 2/3 of all human genes are regulated directly by miRNAs [5], and now over 2500 human miRNAs have been identified [6]. The importance of miRNAs in cancer is suggested as most of them are located at cancer-associated genomic regions [7]. Furthermore, miRNAs are aberrantly expressed in all cancers including lymphoma [8]. There are many causes of dysfunctional expression in cancer including epigenetic deregulation, chromosomal aberrations, aberrant expression of transcription factors that regulate promoters of miRNAs, and factors that change miRNA biosynthesis or function [9].

Lymphoma is a cancer of the lymphatic system (B and T cells) representing the fifth most common cancer type worldwide and affecting more than a million people. The incidence of non-Hodgkin's lymphoma (NHL) has increased 74% in the US, between 1976 and 2001, and since then is the fifth most common form of death from cancer [10]. In this review we consider the role of miRNAs in lymphomas, their use as biomarkers and their potential as therapeutics.

*Address correspondence to this author at the Oncology area, Biodonostia Research Institute, San Sebastián, Spain;
E-mail: charles.lawrie@biodonostia.org

2. ROLE OF MIRNAS IN LYMPHOPOIESIS

Hematopoietic stem cells (HSC) must balance their pluripotency whilst at the same time responding to lineage determining signals. This process is tightly regulated by a network of intrinsic and extrinsic stimuli, transcription factors, signaling pathways, cytokines, growth factors, and other molecular components. MiRNAs can target many of these as well as more generally determining HSC fate, differentiation state, self-renewal ability and function, apoptosis levels, and the balance of lymphoid and myeloid progenitor cells [11].

MiRNAs play a crucial role in hematopoiesis as demonstrated by the deletion of *Dicer1,* which severely inhibited peripheral $CD8^+$ development as well as reducing numbers of $CD4^+$ cells which when stimulated displayed increased apoptosis rates and low proliferatation [12]. However, when *Dicer1* was deleted in $CD34^+$ HSCs an increase in apoptosis occurred along with reduced hematopoietic ability [13], and when deleted in early B cell progenitors the pro to pre B cell transition was blocked as a result of *miR-17~92* targeting of BIM which could be rescued by BCL2 expression [14].

The first study to look at miRNA involvement in lymphocyte development was in 2004, and demonstrated that *miR-223, miR-181* and *miR-142* were highly expressed in B-cells, and that HSCs expressing ectopic *miR-181* significantly increased the numbers of B-cells and cytotoxic CD8+ T-cells in recipient mice [15]. *miR-181* can also regulate levels of CD69, BCL2 and TCRα during T cell development

1875-5488/15 $58.00+.00

[16], and is responsible for T-cell receptor sensitivity [17]. *miR-155* deletion in mice made them immunodeficient, with B cells producing lower immunoglobulin levels after antigen treatment, and T cells producing reduced levels of IFNG and IL2. Both of these effects were mediated by regulation of PU.1 [18]. Activation of B cells or CD4+ T cells *in vitro* can up-regulate *miR-155*, whilst deletion of this miRNA in activated B cells reduces TNF and lymphotoxin levels as well biasing T cell differentiation towards the T_h2 phenotype [19].

Both *miR-155* and *miR-181* are key regulators of germinal centre (GC) B-cell differentiation [20]. Deletion of *Dicer1* in activated B cells reduces GC B-cell formation and consequent B-cells express higher levels of BIM [21]. GC B-cells are characterized by CD10, HGAL, BCL6, and LMO2 expression of the lack of the activated B-cell markers XBP1 or PRDM1/BLIMP1 [22]. *miR-155* directly regulates levels of both HGAL and Rhotekin 2 [23], whilst the *miR-30* family, *miR-9* and *let-7a*, all target BCL6 and PRDM1/BLIMP1 [24]. *miR-223* controls expression of LMO2 [25], and *miR-125b* of PRDM1/BLIMP1 and IRF4 [26]. *miR-155* also regulates PU1 and CD10 modulating activated B-cell formation through NF-kB [27], and *miR-125a/b* can regulate TNFAIP3 promoting activation of NF-kB [28]. The *miR-17-92* cluster is another essential regulator of lymphopoiesis. Targeted deletion of these miRNAs causes blockage of pro- to pre-B cell pathway as a result of BIM inhibition [29]. Members of the *miR-17-92* cluster can also target other key immunomodulatory components including PP2A, PTEN and PRKAA1 [29, 30]. Pro- to pre-B cell development is also regulated by *miR-34a* and *miR-150* via modulation of FOXP1 [31], and MYB respectively [32].

3. B-CELL LYMPHOMAS

As under physiological conditions there is a clear involvement of miRNAs in malignant lymphomagenesis in general. For example, *Dicer1* deletion in a murine myc-lymphoma model decreased the incidence of lymphoma coupled with a change to very early B-cell precursor stage of diesase [33]. Similarly in a p53-null model, *Dicer1* deletion reduced lymphomagenesis and conferred prolonged survival to the mice [34]. Below we discuss the involvement of miRNAs in the most common types of lymphoma.

3.1. Diffuse Large B-cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) represents the most common lymphoid malignancy with an incidence of about 3 per 100,000 people and accounts for nearly 40% all lymphoid tumors [35]. DLBCL was one of the first lymphomas to be linked with aberrant miRNA expression, in particular the observation that *miR-155* is highly expressed in this malignancy [36]. Indeed, forced over-expression of this miRNA in mice results in the development of a high grade B-cell lymphoma similar to DLBCL [37]. Further experimentation has shown that this oncogenicity is mediated by *miR-155* targeting of SHIP1 and C/EBPβ [38]. When *miR-155* was expressed in an inducible manner, although mice developed lymphoma, when the stimulus was removed the tumor quickly disappeared and after one week mice had no measurable disease at all [39]. *In vitro, miR-155* expression suppresses the growth-inhibition of BMP2/4 and TGF-β1 in DLBCL cells via SMAD5 inhibition [40]. It can also regulate the PI3K-AKT pathway via targeting of PIK3R1 [41]. Interestingly it has been demonstrated that SHIP1 is differentially expressed in the two major molecular subtypes of DLBCL (i.e. activated B cell-like (ABC) and germinal center B cell-like (GC)) [42]. This is consistent with identified differences in *miR-155* expression between GC- and ABC-type DLBCL [36b, 36c]. Moreover, CD10, associated with GC-type DLBCL [43], and constitutive NF-κB expression, the hallmark of ABC-type DLBCL [44], are linked through the *miR-155/PU.1* pathway [27]. When mice were inoculated with U2932, an ABC-type DLBCL cell line treatment with exogenous *miR-34a* reduced tumor growth via targeting Foxp1 [45], a molecule associated with ABC-type DLBCL [22]. *miR-34a* is a well described tumor suppressor miRNA that is closely connected with the p53 network in solid tumors [46], and a positive feedback loop exists whereby p53 induces *miR-34a* expression and in turn *miR-34a* activates p53 through SIRT1 inhibition [47].

Over-expression of the *miR-17~92* cluster in a Eμ-myc model resulted in increased aggressiveness of lymphoma development [48]. The MYC/*miR-17-92*/E2F circuit was shown to be responsible for this affect [49], as MYC up-regulates the *miR-17-92* cluster which in turn targets E2F1, whilst conversely pro-proliferative E2F3 regulates the *miR-17-92* cluster [50]. *miR-19* has been identified as the key oncogenic component of the *miR-17-92* cluster and can activate the Akt-mTOR pathway in the Eμ-myc model through PTEN antagonization resulting in the promotion of cell survival [51] (Fig. **1**).

3.2. Follicular Lymphoma (FL)

Despite follicular lymphoma (FL) being the most common indolent lymphoma, there are relatively few studies that have investigated miRNA expression in this disease. In the first of these, the levels of 153 miRNAs were measured in 46 FL samples and compared with DLBCL cases or normal lymph nodes [52]. Shortly afterwards, our group measured the expression levels of 464 miRNAs in 18 cases of FL and 80 cases of DLBCL [53]. In this publication we reported that the levels of six miRNAs (*miR-223, miR-217, miR-222, miR-221, let-7i* and *let-7b*) were differentially expressed between cases of FL that underwent high grade histological transformation compared to those that did not. More recently, the *miR-17~92* cluster has been identified as a useful diagnostic differentiator between the potentially confounding diagnosis of GC-DLBCL and FL (grade 3) [54]. Another study compared FL with nodal marginal zone lymphoma (NMZL) [55], and yet another with follicular hyperplasia [56]. This latter study identified miRNAs associated with FL patients that responded to PACE chemotherapy, as well as showing that p21 and SOCS2 were regulated by *miR-20a/b* and *miR-194* in FL cell lines.

Although >90% of FL cases have the t(14;18) translocation, a minority do not. Interestingly, a recent study identified 17 miRNAs that were differentially expressed between these diseases [57].

3.3. Mantle Cell Lymphoma (MCL)

Although relatively rare, mantle cell lymphoma (MCL) is a particular aggressive lymphoma and the prognostic

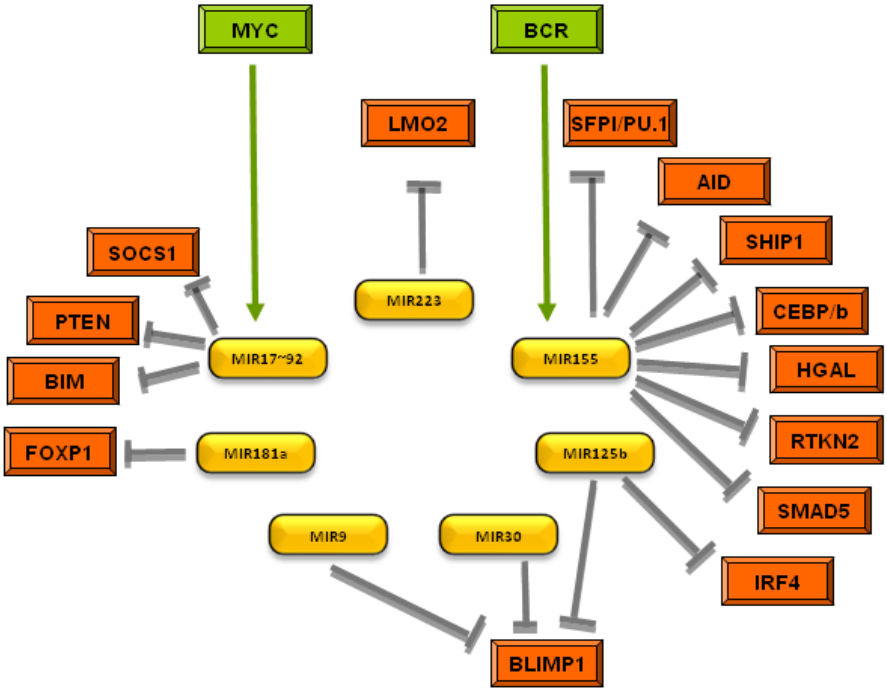

Fig. (1). MiRNA implicated in the pathogenesis of DLBCL and their target genes.

outcome of patients is poor. Several studies have looked at miRNA expression in MCL [58]. The loss of potential miRNA target sites for *miR-15/16* and members of the *miR-17-92* cluster in the 3'UTR of CCND1 are proposed to contribute to the characteristic Cyclin D1 over-expression in MCL [59]. Indeed, over-expression of *miR-17~92* cluster members are correlated with high MYC expression in aggressive MCL [58c]. Similarly a high proliferation gene signature [58d], and activation of the PI3K/AKT pathway, as well as inhibition of chemotherapy-induced apoptosis are found in MCL cell lines [60]. PHLPP2, a key regulator of the PI3K/Akt pathway, has been shown to be targeted by the *miR-17-92* cluster along with PTEN and BIM in MCL [61]. Inhibition of *miR-17-92* expression in a xenotransplant model of MCL inhibited PI3K/Akt pathway and caused decreased tumor growth. Also the inhibition of *miR-29* was demonstrated to activate CDK4/CDK6 in MCL, as well as acting as a potential prognostic marker for this disease [58a].

3.4. Burkitt Lymphoma (BL)

The hallmark of Burkitt lymphoma (BL) is the MYC-IgH (t(8;14)) translocation that results in over-expression of the MYC oncogene. Mice with a mutation in a *miR-155* binding site of the 3´-UTR of the AID gene display increased levels of these translocations [62]. MYC regulates, and in turn itself is regulated by a large number of miRNAs. This results in a complex regulatory loop that is intimately involved in lymphomagenesis [63]. Indeed it has been suggested that MYC over-expression in BL cases without the t(8;14) translocation can be explained by miRNA deregulation [64]. In addition to a functional role, miRNAs could also facilitate classification of the group of B-cell lymphomas with intermediate features between DLBCL and BL [64].

3.5. Hodgkin Lymphoma (HL)

Ribonucleoprotein chromatin immunoprecipitation (RIP-ChIP) was used to look at the involvement of miRNAs Hodgkin lymphoma (HL) HL cell lines [65]. They found an over-representation of genes associated with cell proliferation, apoptosis and the p53 pathway. Elsewhere JAK2 was demonstrated to be regulated by *miR-135a,* and that over-expression increased apoptosis and decreases cell growth via Bcl-xL inhibition in HL cell lines [66]. Furthermore they observed that patients with low *miR-135a* had significantly poorer prognostic outcome. Inhibition of *let-7* and *miR-9* reduced the levels of PRDM1/BLIMP1 in HL cell lines preventing plasma cell differentiation [67]. In another study *miR-9* was shown to target Dicer and HuR in HL. Inhibition of *miR-9* led to a decrease in cytokine production and a reduced ability to attract inflammatory cells [68]. Ectopic administration of a *miR-9* antagomir caused to decreased tumor growth in a xenotransplant model.

3.6. Other B-cell Lymphomas

A number of studies have looked at the role of miRNAs in mucosa-associated lymphoid tissue (MALT) lymphoma. For example, a 27-miRNA signature was identified that could distinguish between gastric DLBCL and MALT lymphoma [69]. This study proposed that the transformation from gastritis to MALT lymphoma is regulated epigenetically by methylation of *miR-203,* leading to the proposition that ABL1 might be a useful druggable target for this malignancy [70]. In another study five miRNAs (*miR-150, miR-550, miR-124a, miR-518b* and *miR-539)* were identified as being differentially expressed in MALT lymphoma compared to gastritis [71]. High E2A levels were found to correlate with increased *miR-223* expression in gastric MALT lymphoma [72]. Finally, a miRNA signature of splenic marginal zone lymphoma (SMZL) cases was reported [73].

4. T-CELL LYMPHOMAS

Compared to their B-cell counterparts, very little is known about miRNA expression in T-cell lymphoma. Our group provided the first functional evidence for miRNAs in T-cell lymphomas in a study on Sézary syndrome (SzS), a rare aggressive primary cutaneous T-cell (CD4(+)) lymphoma [74]. We demonstrated that *miR-342* plays an important pathogenic role in SzS by targeting RANKL which was associated with the protection of SzS cells from apoptosis. The identity of several of the miRNA we identified as being aberrantly expressed have subsequently been validated by other groups since [75]. More recently, further mechanistic insights into the role of miRNA in SzS showed that the widespread deficiency of PTEN observed in SzS might be in part explained by the dysregulation of *miR-21*, *miR-106b*, and *miR-486* [76].

Mycosis fungoides (MF) is a common, indolent primary cutaneous T-cell lymphoma (CTCL), with rare, more aggressive variants. A minority of the MF cases may undergo transformation associated with poor prognosis. Our group have also performed profiling studies on tumor stage MF [77], as well as in cutaneous anaplastic large cell lymphoma (cALCL) [78]. As a result of these, a qRT-PCR based classifier (*miR-155, miR-203* and *miR-205)* has been proposed, able to distinguish between the various forms of cutaneous T-cell lymphomas and related benign disorders [79]. Importantly, both a training (n = 90) and a blinded test (n = 58) cohorts were used in this study. Besides its role in B-cell development, *miR-150* also regulates NK cells via Myb targeting [80], as well as other T-cell subsets through NOTCH3 inhibition [81]. Transfection of *miR-150* into NK/T cell lymphoma cell lines increased apoptosis and decreased cell proliferation. These effects were mediated via DKC1 and AKT2targeting, and caused a decrease in BIM, p53 and phospho-AKT levels. In addition, over-expression of *miR-155* and *miR-21* was shown to activate the PI3K-Akt pathway in NK/T-cell lymphomas [38c]. Also, over-expression of *miR-122* in CTCL induced AKT phosphorylation linked to a decreased sensitivity to chemotherapy-induced apoptosis, as well as inhibiting p53 expression [82].

5. MIRNAS AS BIOMARKERS OF LYMPHOID MALIGNANCIES

The first demonstration that miRNAs could be useful as diagnostic biomarkers came from the 2002 groundbreaking publication of Calin and co-workers*,* who made the connection between the frequently deleted 13q14 locus, and the down-regulation of the *miR-15a/16* cluster that is encoded within this region in chronic lymphocytic leukaemia (CLL) patients [83]. Two years later, miRNAs were first demonstrated as prognostic biomarkers in lung cancer patients [84]. Since then, the speed of miRNA cancer biomarker discovery has been quite astonishing with over 9600 publications to date (source: Pubmed search (15/03/15) string= "(microRNA AND cancer) AND (prognosis OR diagnosis OR biomarker)"). The potential of miRNAs as cancer (diagnostic) biomarkers is obvious as particular miRNA expression profiles can distinguish cancers according to diagnosis and developmental stage of the tumor to a greater degree of accuracy than traditional gene expression analysis, even discriminating between cancers that are poorly separated histologically [85]. This ability is especially attractive to the field of B-cell lymphomas, a group of more than 35 recognized neoplasms [86] classified largely on the basis of immunohistochemical staining patterns, that are often challenging to accurately diagnose [87]. The usefulness of molecular methods to complement traditional morphological classifications in B-cell lymphoma is exemplified by DLBCL, where gene expression profiling has led to the identification of least two distinct subtypes that are prognostically and mechanistically very different, and respond differently to treatment [42, 88] (Table **1**).

5.1. miRNAs As Non-invasive Biomarkers of B-cell Lymphoma

An additional feature of miRNAs that make them attractive candidates as cancer biomarkers is that they are much more stable than other RNA species and, as a result, can be purified and measured easily in routinely prepared formalin-fixed paraffin embedded (FFPE) biopsy material [36b] and biological fluids such as blood or its derivatives (sera, plasma) [89]. The standard protocol for many cancers (including lymphoma) diagnosis remains the histopathological inspection of tumor material obtained by invasive biopsy; a procedure that is rather frequently expensive, uncomfortable and sometimes risky for patients. Therefore there has been great interest in the field of circulating nucleic acids in blood as non-invasive cancer biomarkers [90]. An additional benefit of blood-based testing is the capability to perform screening and repeat sampling on patients undergoing therapy, or monitoring disease progression allowing for the development of a personalised approach to cancer patient management. Unlike other RNA molecules, the vast majority of which are degraded by high levels of RNases found in the blood [91], miRNAs seem to be stable in the blood and are surprisingly resistant to fragmentation by either chemical or enzymatic agents [92].

In 2007 we first reported the presence of miRNAs in the blood of lymphoma patients [93] and in 2008 demonstrated the up-regulation of *miR-155* and *miR-210* in the blood (sera) of DLBCL patients compared to healthy controls, as well as the prognostic potential of *miR-21* [94], an observation validated independently some years later [95]. In addition to confirming the up-regulation of *miR-155* in DLBCL sera, another study also reported up-regulation of *miR-15a, miR-16* and *miR-29c,* and down-regulation of *miR-34a* [96]. A third study, this time in plasma rather than sera, observed reduced levels of *miR*-92 that varied in response to chemotherapy in DLBCL, FL and T-cell non-Hodgkins lymphoma patients [97]. Similarly, plasma levels of *miR-92a* have been proposed as diagnostic/prognostic biomarkers for multiple myeloma (MM) [97, 98].

In HL patient, plasma levels of *miR-494* and *miR-1973* were identified as indicators of both relapse and interim therapy response [99]. In addition, plasma *miR-221* has been found to be a good diagnostic and prognostic marker for extranodal natural killer T-Cell NK/Tcell lymphoma [100].

Clearly although results are very preliminary, the ability of miRNAs to act as non-invasive biomarkers of B-cell lymphomas is a promising prospect (Table **1**).

Table 1. Examples of deregulated ncRNAs in relationship with their potential as biomarkers in various lymphoma types.

Lymphoma	miRNA	Biomarker Type	Sample Source	Cohort Size		*P*-value	Reference
				Cases	Controls		
DLBCL	*miR-155* *miR-210* *miR-21*	D	Serum	60	43	0.009 0.02 0.04	[94]
	miR-21	D, P	Serum	62	50	< 0.001	[106]
	miR-15a, miR-16-1, miR-29c, miR-34a, miR-155	D	Serum	75	77	< 0.05	[96]
	miR-155	PR	Biopsy	79	-	0.0008	[102]
	miR-18a *miR-181a* *miR-222*	P	Biopsy	176	-	0.038 0.026 0.004	[101]
	SNORA48, miR-106b, miR-106b, miR-1181, miR-124, miR-1299, miR-25*, miR-33b*, miR-432, miR-551b*, miR-629, miR-652, miR-654-3p, miR-671-5p, miR-766, miR-877*, miR-93, miR-93**	PR	Biopsy	116	-	0.03	[107]
FL	*miR-9, miR-9*, miR-301, miR-338, miR-213*	D	Biopsy	46	7	NA	[52]
	miR-223, miR-217, miR-222, miR-221, let-7i, let-7b	P	Biopsy	7	11	< 0.05	[53]
MCL	*miR-29*	P	Biopsy	30	-	0.04	[58a]
HL	*miR-494, miR-1973, miR-21*	D	Plasma	42	20	0.004 0.007 < 0.0001	[99]
	miR-135a	P	Biopsy	89	-	0.04	[66]
	miR-21, miR-30e, miR-30d, miR-92b	P, PR	Biopsy	29	-	< 0.001	[108]
MALT	*miR-150, miR-550, miR-124a, miR-518b, miR-539*	D	Biopsy	NA	NA	< 0.001	[71]
SzS	*miR-150, miR-191, miR-15a, miR-16*	D	PBMCs	36	12	0.04	[109]
	miR-21 *miR-214* *miR-486*	P	PBMCs	23	-	0.03 0.004 0.0038	[75b]
MF	*miR-155* *miR-92a* *miR-93*	D	Biopsy	19	12	0.014 0.001 0.001	[77]
NK/T-cell	*miR-221*	D, P	Plasma	79	37	0.038	[100]

ncRNA, non-coding RNA; miR, microRNA; SNOR, small nucleolar RNAs; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma; SzS, Sézary syndrome; MF, mycosis fungoides; NK/T-cell, extra-nodal natural killer T-Cell (NK/T-cell) lymphoma; D, Diagnostic Biomarker; P, prognostic Biomarker; PR, Predictive of response to treatment Biomarker; MV, microvesicles; PBMCs, peripheral blood monuclear cells; NA, not available.

6. MIRNAS AS PREDICTIVE MARKERS OF RESPONSE AND POTENTIAL THERAPEUTIC USES

Recently, miRNA profiling of different B-cell lymphomas has been shown to be useful beyond the mere classification of different lymphoma entities. For example, a 6-gene model combined with the international prognostic index (IPI) and with a three-miRNA expression signature could predict patients' outcome in a series of 176 uniformly treated DLBCL cases, and correlated the results to survival [101]. More recently, Iqbal and collaborators have found a predictive miRNA signature in DLBCL, associated with R-CHOP

response failure. This signature included high expression levels of *miR-155,* as we have previously reported [53]. Furthermore, *in vitro* overexpression of *miR-155* sensitized cells to AKT inhibitors, suggesting a novel treatment option for resistant DLBCL [102].

Indeed, probably the most promising clinical aspect of miRNAs is their potential as novel therapeutic molecules, either as a tool to modulate target genes associated with disease, or by correcting dysfunctional expression of the miRNAs themselves. The former approach is particularly attractive because a single miRNA can be used against multiple components of a disease pathway or even against the pathway in its entirety [103]. There are two major strategies to therapeutically modulate deregulated miRNAs in cancer; the first to use miRNA mimics to restore physiological levels of miRNAs that are down-regulated for example tumor suppressor miRNAs such as *miR-34 or let-7.* A second strategy is to use inhibitors of over-expressed miRNAs for example directed against so-called oncomirs such as *miR-21* or *miR-155* [39, 104].

There now exists a wealth of *in vivo* animal evidence that have provided the proof-of-principle of the therapeutic efficacy of miRNAs in disease; however, at present all but a couple of these studies remain at the pre-clinical stage. Translating these results into the clinic need first addressing a few major issues, such as the effective targeting of therapy (e.g. tissue-specific delivery, dosage and pharmacodynamics), as well as safety concerns (e.g. off-target effects, RNA-mediated immunostimulation and the use of viral vectors etc.). Indeed, although a number of strategies to deliver miRNA in experimental models have been used in research, clinically applicable tools for gene delivery are limited and currently are focused on retroviral-based or adenoviral-based vectors.

In addition to viral vector-based gene therapy, synthetic miRNA has also been used in gain-of-function assays. These miRNA mimics are small, chemically modified RNA molecules that resemble endogenous mature miRNA molecules that are commercially available [105]. By the use of formulated synthetic miRNA, the therapeutic potential of exogenous *miR-34a* against human multiple myeloma cells *in vitro* and *in vivo* has been successful in preclinical models. This favorable outcome is a proof of concept that supports the use of formulated *miR-34a* based treatment strategies in patients [104a]. MiRNA mimics have no vector-based toxicity; therefore, if their delivery agents do not cause side effects over long-term use, they can be a promising therapeutic approach for tumors.

That said, this is an area very much still in its infancy that is almost certain to flourish in the near future as the field matures, and promises to add to the current battery of therapies available to clinicians in the continual fight against lymphoma.

7. CONCLUSION AND FUTURE DIRECTIONS

Over the last years, a number of studies have underlined the key role that miRNAs have in lymphoma, both in B-cell and in T-cell malignancies. They interfere with multiple pathways involved in cell cycle, tumor growth and apoptosis, acting as tumor suppressor or oncogenes. Interestingly, different lymphoma subtypes have distinct miRNAs expression profiles. Their ability to improve histological classification and their stability in body fluids make them ideal biomarkers. Further studies and clinical trials are needed to confirm the prognostic and predictive power of miRNAs, as well as to test the miRNAs and their blocking molecules as a therapeutic approach for lymphoma.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We apologize to the authors of the many studies that were not included in this review due to space limitations. CHL and his research are supported by funding from the Starmer-Smith memorial lymphoma Fund, Ikerbasque (the Basque Foundation for Science), MINECO (Spanish Ministry in charge of R&D&i), Gobierno Vasco and Diputación Foral de Gipuzkoa. MFM is supported by the Asociación Española Contra el Cáncer (AECC).

REFERENCES

[1] Crick, F. Central dogma of molecular biology. *Nature,* **1970,** *227* (5258), 561-3.

[2] Mattick, J.S. Non-coding RNAs: the architects of eukaryotic complexity. *EMBO Rep.,* **2001,** *2* (11), 986-91.

[3] Lee, R. C.; Ambros, V. An extensive class of small RNAs in Caenorhabditis elegans. *Science,* **2001,** *294* (5543), 862-4.

[4] Kim, V.N. MicroRNA biogenesis: coordinated cropping and dicing. *Nat. Rev. Mol. Cell Biol.,* **2005,** *6* (5), 376-85.

[5] Friedman, R.C.; Farh, K.K.; Burge, C.B.; Bartel, D.P. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res.,* **2009,** *19* (1), 92-105.

[6] Griffiths-Jones, S.; Grocock, R.J.; van Dongen, S.; Bateman, A.; Enright, A.J. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Res.,* **2006,** *34* (Database issue), D140-4.

[7] Calin, G.A.; Sevignani, C.; Dumitru, C.D.; Hyslop, T.; Noch, E.; Yendamuri, S.; Shimizu, M.; Rattan, S.; Bullrich, F.; Negrini, M.; Croce, C.M. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. USA,* **2004,** *101* (9), 2999-3004.

[8] (a) Lawrie, C.H. microRNA expression in lymphoid malignancies: new hope for diagnosis and therapy? *J. Cell Mol. Med.,* **2008,** *12* (5A), 1432-44; (b) Iorio, M.V.; Croce, C.M. MicroRNAs in cancer: small molecules with a huge impact. *J. Clin. Oncol.,* **2009,** *27* (34), 5848-56.

[9] Croce, C.M. Causes and consequences of microRNA dysregulation in cancer. *Nat. Rev. Genet.,* **2009,** *10* (10), 704-14.

[10] SEER Cancer Statistics Review, 1975-2002. *National Cancer Institute,* **2005**.

[11] Georgantas, R.W., 3rd; Hildreth, R.; Morisot, S.; Alder, J.; Liu, C.G.; Heimfeld, S.; Calin, G.A.; Croce, C.M.; Civin, C.I. CD34+ hematopoietic stem-progenitor cell microRNA expression and function: A circuit diagram of differentiation control. *Proc. Natl. Acad. Sci. USA,* **2007,** *104* (8), 2750-2755.

[12] (a) Cobb, B.S.; Nesterova, T.B.; Thompson, E.; Hertweck, A.; O'Connor, E.; Godwin, J.; Wilson, C.B.; Brockdorff, N.; Fisher, A. G.; Smale, S.T.; Merkenschlager, M. T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. *J. Exp. Med.,* **2005,** *201* (9), 1367-73; (b) Muljo, S.A.; Ansel, K. M.; Kanellopoulou, C.; Livingston, D.M.; Rao, A.; Rajewsky, K. Aberrant T cell differentiation in the absence of Dicer. *J. Exp. Med.,* **2005,** *202* (2), 261-9.

[13] Guo, S.; Lu, J.; Schlanger, R.; Zhang, H.; Wang, J.Y.; Fox, M.C.; Purton, L.E.; Fleming, H.H.; Cobb, B.; Merkenschlager, M.; Golub, T.R.; Scadden, D.T. MicroRNA miR-125a controls hema-

topoietic stem cell number. *Proc. Natl. Acad. Sci. USA,* **2010,** *107* (32), 14229-34.

[14] Koralov, S.B.; Muljo, S.A.; Galler, G.R.; Krek, A.; Chakraborty, T.; Kanellopoulou, C.; Jensen, K.; Cobb, B.S.; Merkenschlager, M.; Rajewsky, N.; Rajewsky, K. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. *Cell,* **2008,** *132* (5), 860-74.

[15] Chen, C.Z.; Li, L.; Lodish, H.F.; Bartel, D.P. MicroRNAs modulate hematopoietic lineage differentiation. *Science,* **2004,** *303* (5654), 83-6.

[16] Neilson, J.R.; Zheng, G.X.; Burge, C.B.; Sharp, P.A. Dynamic regulation of miRNA expression in ordered stages of cellular development. *Genes Dev.,* **2007,** *21* (5), 578-89.

[17] Li, Q.J.; Chau, J.; Ebert, P.J.; Sylvester, G.; Min, H.; Liu, G.; Braich, R.; Manoharan, M.; Soutschek, J.; Skare, P.; Klein, L.O.; Davis, M.M.; Chen, C.Z. miR-181a is an intrinsic modulator of T cell sensitivity and selection. *Cell,* **2007,** *129* (1), 147-61.

[18] (a) Rodriguez, A.; Vigorito, E.; Clare, S.; Warren, M.V.; Couttet, P.; Soond, D.R.; van Dongen, S.; Grocock, R.J.; Das, P.P.; Miska, E.A.; Vetrie, D.; Okkenhaug, K.; Enright, A. J.; Dougan, G.; Turner, M.; Bradley, A. Requirement of bic/microRNA-155 for normal immune function. *Science,* **2007,** *316* (5824), 608-11; (b) Thai, T.H.; Calado, D.P.; Casola, S.; Ansel, K.M.; Xiao, C.; Xue, Y.; Murphy, A.; Frendewey, D.; Valenzuela, D.; Kutok, J. L.; Schmidt-Supprian, M.; Rajewsky, N.; Yancopoulos, G.; Rao, A.; Rajewsky, K. Regulation of the germinal center response by microRNA-155. *Science,* **2007,** *316* (5824), 604-8.

[19] Vigorito, E.; Perks, K.L.; Abreu-Goodger, C.; Bunting, S.; Xiang, Z.; Kohlhaas, S.; Das, P.P.; Miska, E.A.; Rodriguez, A.; Bradley, A.; Smith, K.G.; Rada, C.; Enright, A. J.; Toellner, K. M.; Maclennan, I. C.; Turner, M. microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. *Immunity,* **2007,** *27* (6), 847-59.

[20] (a) de Yebenes, V.G.; Belver, L.; Pisano, D.G.; Gonzalez, S.; Villasante, A.; Croce, C.; He, L.; Ramiro, A.R. miR-181b negatively regulates activation-induced cytidine deaminase in B cells. *J. Exp. Med.,* **2008,** *205* (10), 2199-206; (b) Teng, G.; Hakimpour, P.; Landgraf, P.; Rice, A.; Tuschl, T.; Casellas, R.; Papavasiliou, F.N. MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. *Immunity,* **2008,** *28* (5), 621-9.

[21] Xu, S.; Guo, K.; Zeng, Q.; Huo, J.; Lam, K.P. The RNase III enzyme Dicer is essential for germinal center B-cell formation. *Blood* **2012,** *119* (3), 767-76.

[22] Choi, W.W.; Weisenburger, D.D.; Greiner, T.C.; Piris, M.A.; Banham, A.H.; Delabie, J.; Braziel, R.M.; Geng, H.; Iqbal, J.; Lenz, G.; Vose, J.M.; Hans, C.P.; Fu, K.; Smith, L.M.; Li, M.; Liu, Z.; Gascoyne, R.D.; Rosenwald, A.; Ott, G.; Rimsza, L.M.; Campo, E.; Jaffe, E.S.; Jaye, D.L.; Staudt, L.M.; Chan, W.C.A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. *Clin. Cancer Res.,* **2009,** *15* (17), 5494-502.

[23] Dagan, L.N.; Jiang, X.; Bhatt, S.; Cubedo, E.; Rajewsky, K.; Lossos, I.S. miR-155 regulates HGAL expression and increases lymphoma cell motility. *Blood,* **2012,** *119* (2), 513-20.

[24] Lin, J.; Lwin, T.; Zhao, J.J.; Tam, W.; Choi, Y.S.; Moscinski, L. C.; Dalton, W.S.; Sotomayor, E. M.; Wright, K. L.; Tao, J. Follicular dendritic cell-induced microRNA-mediated upregulation of PRDM1 and downregulation of BCL-6 in non-Hodgkin's B-cell lymphomas. *Leukemia,* **2011,** *25* (1), 145-52.

[25] Gururajan, M.; Haga, C.L.; Das, S.; Leu, C.M.; Hodson, D.; Josson, S.; Turner, M.; Cooper, M.D. MicroRNA 125b inhibition of B cell differentiation in germinal centers. *Int. Immunol.,* **2010,** *22* (7), 583-92.

[26] Malumbres, R.; Sarosiek, K.A.; Cubedo, E.; Ruiz, J.W.; Jiang, X.; Gascoyne, R.D.; Tibshirani, R.; Lossos, I. S. Differentiation stage-specific expression of microRNAs in B lymphocytes and diffuse large B-cell lymphomas. *Blood,* **2009,** *113* (16), 3754-64.

[27] Thompson, R.C.; Herscovitch, M.; Zhao, I.; Ford, T.J.; Gilmore, T. D. NF-kappaB down-regulates expression of the B-lymphoma marker CD10 through a miR-155/PU.1 pathway. *J. Biol. Chem.,* **2011,** *286* (3), 1675-82.

[28] Kim, S.W.; Ramasamy, K.; Bouamar, H.; Lin, A.P.; Jiang, D.; Aguiar, R.C. MicroRNAs miR-125a and miR-125b constitutively activate the NF-kappaB pathway by targeting the tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20). *Proc. Natl. Acad. Sci. USA,* **2012,** *109* (20), 7865-70.

[29] Ventura, A.; Young, A.G.; Winslow, M.M.; Lintault, L.; Meissner, A.; Erkeland, S.J.; Newman, J.; Bronson, R.T.; Crowley, D.; Stone, J.R.; Jaenisch, R.; Sharp, P.A.; Jacks, T. Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. *Cell,* **2008,** *132* (5), 875-86.

[30] (a) Xiao, C.; Srinivasan, L.; Calado, D.P.; Patterson, H.C.; Zhang, B.; Wang, J.; Henderson, J.M.; Kutok, J.L.; Rajewsky, K. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat. Immunol.,* **2008,** *9* (4), 405-14; (b) Mu, P.; Han, Y.C.; Betel, D.; Yao, E.; Squatrito, M.; Ogrodowski, P.; de Stanchina, E.; D'Andrea, A.; Sander, C.; Ventura, A. Genetic dissection of the miR-17~92 cluster of microRNAs in Myc-induced B-cell lymphomas. *Genes Dev.,* **2009,** *23* (24), 2806-11; (c) Mavrakis, K.J.; Wolfe, A.L.; Oricchio, E.; Palomero, T.; de Keersmaecker, K.; McJunkin, K.; Zuber, J.; James, T.; Khan, A.A.; Leslie, C.S.; Parker, J.S.; Paddison, P.J.; Tam, W.; Ferrando, A.; Wendel, H.G. Genome-wide RNA-mediated interference screen identifies miR-19 targets in Notch-induced T-cell acute lymphoblastic leukaemia. *Nat. Cell Biol.,* **2010,** *12* (4), 372-9.

[31] Rao, D.S.; O'Connell, R.M.; Chaudhuri, A.A.; Garcia-Flores, Y.; Geiger, T.L.; Baltimore, D. MicroRNA-34a perturbs B lymphocyte development by repressing the forkhead box transcription factor Foxp1. *Immunity,* **2010,** *33* (1), 48-59.

[32] Zhou, B.; Wang, S.; Mayr, C.; Bartel, D.P.; Lodish, H.F. miR-150, a microRNA expressed in mature B and T cells, blocks early B cell development when expressed prematurely. *Proc. Natl. Acad. Sci. USA,* **2007,** *104* (17), 7080-5.

[33] Arrate, M.P.; Vincent, T.; Odvody, J.; Kar, R.; Jones, S.N.; Eischen, C.M. MicroRNA biogenesis is required for Myc-induced B-cell lymphoma development and survival. *Cancer Res.,* **2010,** *70* (14), 6083-92.

[34] Adams, C.M.; Eischen, C.M. Inactivation of p53 is insufficient to allow B cells and B-cell lymphomas to survive without Dicer. *Cancer Res.,* **2014,** *74* (14), 3923-34.

[35] Coiffier, B. Diffuse large cell lymphoma. *Curr. Opin. Oncol.,* **2001,** *13* (5), 325-34.

[36] (a) Kluiver, J.; Poppema, S.; de Jong, D.; Blokzijl, T.; Harms, G.; Jacobs, S.; Kroesen, B.J.; van den Berg, A. BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. *J. Pathol.,* **2005,** *207* (2), 243-9; (b) Lawrie, C. H.; Soneji, S.; Marafioti, T.; Cooper, C.D.; Palazzo, S.; Paterson, J. C.; Cattan, H.; Enver, T.; Mager, R.; Boultwood, J.; Wainscoat, J. S.; Hatton, C.S. MicroRNA expression distinguishes between germinal center B cell-like and activated B cell-like subtypes of diffuse large B cell lymphoma. *Int. J. Cancer,* **2007,** *121* (5), 1156-61; (c) Eis, P.S.; Tam, W.; Sun, L.; Chadburn, A.; Li, Z.; Gomez, M.F.; Lund, E.; Dahlberg, J.E. Accumulation of miR-155 and BIC RNA in human B cell lymphomas. *Proc. Natl. Acad. Sci. USA,* **2005,** *102* (10), 3627-32.

[37] Costinean, S.; Zanesi, N.; Pekarsky, Y.; Tili, E.; Volinia, S.; Heerema, N.; Croce, C.M. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. *Proc. Natl. Acad. Sci. USA,* **2006,** *103* (18), 7024-9.

[38] (a) O'Connell, R.M.; Chaudhuri, A.A.; Rao, D.S.; Baltimore, D. Inositol phosphatase SHIP1 is a primary target of miR-155. *Proc. Natl. Acad. Sci. USA,* **2009,** *106* (17), 7113-8; (b) Pedersen, I. M.; Otero, D.; Kao, E.; Miletic, A.V.; Hother, C.; Ralfkiaer, E.; Rickert, R.C.; Gronbaek, K.; David, M. Onco-miR-155 targets SHIP1 to promote TNFalpha-dependent growth of B cell lymphomas. *EMBO Mol. Med.,* **2009,** *1* (5), 288-95; (c) Yamanaka, Y.; Tagawa, H.; Takahashi, N.; Watanabe, A.; Guo, Y.M.; Iwamoto, K.; Yamashita, J.; Saitoh, H.; Kameoka, Y.; Shimizu, N.; Ichinohasama, R.; Sawada, K. Aberrant overexpression of microRNAs activate AKT signaling via down-regulation of tumor suppressors in natural killer-cell lymphoma/leukemia. *Blood,* **2009,** *114* (15), 3265-75.

[39] Babar, I.A.; Cheng, C.J.; Booth, C.J.; Liang, X.; Weidhaas, J.B.; Saltzman, W.M.; Slack, F.J. Nanoparticle-based therapy in an *in vivo* microRNA-155 (miR-155)-dependent mouse model of lymphoma. *Proc. Natl. Acad. Sci. USA,* **2012,** *109* (26), E1695-704.

[40] Rai, D.; Kim, S.W.; McKeller, M.R.; Dahia, P.L.; Aguiar, R.C. Targeting of SMAD5 links microRNA-155 to the TGF-beta pathway and lymphomagenesis. *Proc. Natl. Acad. Sci. USA,* **2010,** *107* (7), 3111-6.

[41] Huang, X.; Shen, Y.; Liu, M.; Bi, C.; Jiang, C.; Iqbal, J.; McKeithan, T.W.; Chan, W.C.; Ding, S.J.; Fu, K. Quantitative Proteomics

Reveals that miR-155 Regulates the PI3K-AKT Pathway in Diffuse Large B-Cell Lymphoma. *Am. J. Pathol.,* **2012,** *181* (1), 26-33.

[42] Alizadeh, A.A.; Eisen, M.B.; Davis, R.E.; Ma, C.; Lossos, I.S.; Rosenwald, A.; Boldrick, J.C.; Sabet, H.; Tran, T.; Yu, X.; Powell, J.I.; Yang, L.; Marti, G.E.; Moore, T.; Hudson, J., Jr.; Lu, L.; Lewis, D.B.; Tibshirani, R.; Sherlock, G.; Chan, W.C.; Greiner, T.C.; Weisenburger, D.D.; Armitage, J.O.; Warnke, R.; Levy, R.; Wilson, W.; Grever, M.R.; Byrd, J.C.; Botstein, D.; Brown, P.O.; Staudt, L.M. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature,* **2000,** *403* (6769), 503-11.

[43] Hans, C.P.; Weisenburger, D.D.; Greiner, T.C.; Gascoyne, R.D.; Delabie, J.; Ott, G.; Muller-Hermelink, H.K.; Campo, E.; Braziel, R.M.; Jaffe, E.S.; Pan, Z.; Farinha, P.; Smith, L.M.; Falini, B.; Banham, A.H.; Rosenwald, A.; Staudt, L.M.; Connors, J.M.; Armitage, J.O.; Chan, W.C. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood,* **2004,** *103* (1), 275-82.

[44] Compagno, M.; Lim, W.K.; Grunn, A.; Nandula, S.V.; Brahmachary, M.; Shen, Q.; Bertoni, F.; Ponzoni, M.; Scandurra, M.; Califano, A.; Bhagat, G.; Chadburn, A.; Dalla-Favera, R.; Pasqualucci, L. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. *Nature,* **2009,** *459* (7247), 717-21.

[45] Craig, V.J.; Tzankov, A.; Flori, M.; Schmid, C.A.; Bader, A.G.; Muller, A. Systemic microRNA-34a delivery induces apoptosis and abrogates growth of diffuse large B-cell lymphoma *in vivo*. *Leukemia,* **2012**. *26* (11), 2421-4

[46] He, L.; He, X.; Lim, L.P.; de Stanchina, E.; Xuan, Z.; Liang, Y.; Xue, W.; Zender, L.; Magnus, J.; Ridzon, D.; Jackson, A.L.; Linsley, P.S.; Chen, C.; Lowe, S.W.; Cleary, M.A.; Hannon, G.J.A microRNA component of the p53 tumour suppressor network. *Nature,* **2007,** *447* (7148), 1130-4.

[47] Yamakuchi, M.; Lowenstein, C.J. MiR-34, SIRT1 and p53: the feedback loop. *Cell Cycle,* **2009,** *8* (5), 712-5.

[48] (a) He, L.; Thomson, J.M.; Hemann, M.T.; Hernando-Monge, E.; Mu, D.; Goodson, S.; Powers, S.; Cordon-Cardo, C.; Lowe, S.W.; Hannon, G.J.; Hammond, S.M.A microRNA polycistron as a potential human oncogene. *Nature,* **2005,** *435* (7043), 828-33; (b) Tagawa, H.; Karube, K.; Tsuzuki, S.; Ohshima, K.; Seto, M. Synergistic action of the microRNA-17 polycistron and Myc in aggressive cancer development. *Cancer Sci.,* **2007,** *98* (9), 1482-90.

[49] O'Donnell, K.A.; Wentzel, E.A.; Zeller, K.I.; Dang, C.V.; Mendell, J.T. c-Myc-regulated microRNAs modulate E2F1 expression. *Nature,* **2005,** *435* (7043), 839-43.

[50] Woods, K.; Thomson, J.M.; Hammond, S.M. Direct regulation of an oncogenic micro-RNA cluster by E2F transcription factors. *J. Biol. Chem.,* **2007,** *282* (4), 2130-4.

[51] Olive, V.; Bennett, M.J.; Walker, J.C.; Ma, C.; Jiang, I.; Cordon-Cardo, C.; Li, Q.J.; Lowe, S.W.; Hannon, G.J.; He, L. miR-19 is a key oncogenic component of mir-17-92. *Genes Dev.,* **2009,** *23* (24), 2839-49.

[52] Roehle, A.; Hoefig, K.P.; Repsilber, D.; Thorns, C.; Ziepert, M.; Wesche, K.O.; Thiere, M.; Loeffler, M.; Klapper, W.; Pfreundschuh, M.; Matolcsy, A.; Bernd, H.W.; Reiniger, L.; Merz, H.; Feller, A. C. MicroRNA signatures characterize diffuse large B-cell lymphomas and follicular lymphomas. *Br. J. Haematol.,* **2008,** *142* (5), 732-44.

[53] Lawrie, C.H.; Chi, J.; Taylor, S.; Tramonti, D.; Ballabio, E.; Palazzo, S.; Saunders, N.J.; Pezzella, F.; Boultwood, J.; Wainscoat, J.S.; Hatton, C.S. Expression of microRNAs in diffuse large B cell lymphoma is associated with immunophenotype, survival and transformation from follicular lymphoma. *J. Cell Mol. Med.,* **2009,** *13* (7), 1248-60.

[54] Fassina, A.; Marino, F.; Siri, M.; Zambello, R.; Ventura, L.; Fassan, M.; Simonato, F.; Cappellesso, R. The miR-17-92 microRNA cluster: a novel diagnostic tool in large B-cell malignancies. *Lab. Invest.,* **2012,** *92* (11), 1574-82.

[55] Arribas, A.J.; Campos-Martin, Y.; Gomez-Abad, C.; Algara, P.; Sanchez-Beato, M.; Rodriguez-Pinilla, M.S.; Montes-Moreno, S.; Martinez, N.; Alves-Ferreira, J.; Piris, M.A.; Mollejo, M. Nodal marginal zone lymphoma: gene expression and miRNA profiling identify diagnostic markers and potential therapeutic targets. *Blood,* **2012,** *119* (3), e9-e21.

[56] Wang, W.; Corrigan-Cummins, M.; Hudson, J.; Maric, I.; Simakova, O.; Neelapu, S.S.; Kwak, L.W.; Janik, J.E.; Gause, B.; Jaffe, E.S.; Calvo, K.R. MicroRNA profiling of follicular lymphoma identifies microRNAs related to cell proliferation and tumor response. *Haematologica,* **2012,** *97* (4), 586-94.

[57] Leich, E.; Zamo, A.; Horn, H.; Haralambieva, E.; Puppe, B.; Gascoyne, R.D.; Chan, W.C.; Braziel, R.M.; Rimsza, L.M.; Weisenburger, D.D.; Delabie, J.; Jaffe, E.S.; Fitzgibbon, J.; Staudt, L.M.; Mueller-Hermelink, H.K.; Calaminici, M.; Campo, E.; Ott, G.; Hernandez, L.; Rosenwald, A. MicroRNA profiles of t(14;18)-negative follicular lymphoma support a late germinal center B-cell phenotype. *Blood,* **2011,** *118* (20), 5550-8.

[58] (a) Zhao, J.J.; Lin, J.; Lwin, T.; Yang, H.; Guo, J.; Kong, W.; Dessureault, S.; Moscinski, L.C.; Rezania, D.; Dalton, W.S.; Sotomayor, E.; Tao, J.; Cheng, J.Q. microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma. *Blood,* **2010,** *115* (13), 2630-9; (b) Di Lisio, L.; Gomez-Lopez, G.; Sanchez-Beato, M.; Gomez-Abad, C.; Rodriguez, M.E.; Villuendas, R.; Ferreira, B.I.; Carro, A.; Rico, D.; Mollejo, M.; Martinez, M.A.; Menarguez, J.; Diaz-Alderete, A.; Gil, J.; Cigudosa, J. C.; Pisano, D.G.; Piris, M.A.; Martinez, N. Mantle cell lymphoma: transcriptional regulation by microRNAs. *Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K.* **2010,** *24* (7), 1335-42; (c) Navarro, A.; Bea, S.; Fernandez, V.; Prieto, M.; Salaverria, I.; Jares, P.; Hartmann, E.; Mozos, A.; Lopez-Guillermo, A.; Villamor, N.; Colomer, D.; Puig, X.; Ott, G.; Sole, F.; Serrano, S.; Rosenwald, A.; Campo, E.; Hernandez, L. MicroRNA expression, chromosomal alterations, and immunoglobulin variable heavy chain hypermutations in Mantle cell lymphomas. *Cancer Res.,* **2009,** *69* (17), 7071-8; (d) Iqbal, J.; Shen, Y.; Liu, Y.; Fu, K.; Jaffe, E.S.; Liu, C.; Liu, Z.; Lachel, C.M.; Deffenbacher, K.; Greiner, T.C.; Vose, J.M.; Bhagavathi, S.; Staudt, L. M.; Rimsza, L.; Rosenwald, A.; Ott, G.; Delabie, J.; Campo, E.; Braziel, R.M.; Cook, J.R.; Tubbs, R.R.; Gascoyne, R.D.; Armitage, J.O.; Weisenburger, D.D.; McKeithan, T.W.; Chan, W.C. Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. *Blood,* **2012,** *119* (21), 4939-48.

[59] (a) Chen, R.W.; Bemis, L.T.; Amato, C.M.; Myint, H.; Tran, H.; Birks, D.K.; Eckhardt, S.G.; Robinson, W.A. Truncation in CCND1 mRNA alters miR-16-1 regulation in mantle cell lymphoma. *Blood,* **2008,** *112* (3), 822-9; (b) Deshpande, A.; Pastore, A.; Deshpande, A.J.; Zimmermann, Y.; Hutter, G.; Weinkauf, M.; Buske, C.; Hiddemann, W.; Dreyling, M. 3'UTR mediated regulation of the cyclin D1 proto-oncogene. *Cell Cycle,* **2009,** *8* (21), 3584-92.

[60] Chaudhuri, A.A.; So, A.Y.; Mehta, A.; Minisandram, A.; Sinha, N.; Jonsson, V.D.; Rao, D.S.; O'Connell, R.M.; Baltimore, D. Oncomir miR-125b regulates hematopoiesis by targeting the gene Lin28A. *Proc. Natl. Acad. Sci. USA,* **2012,** *109* (11), 4233-8.

[61] Rao, E.; Jiang, C.; Ji, M.; Huang, X.; Iqbal, J.; Lenz, G.; Wright, G.; Staudt, L.M.; Zhao, Y.; McKeithan, T.W.; Chan, W.C.; Fu, K. The miRNA-17 approximately 92 cluster mediates chemoresistance and enhances tumor growth in mantle cell lymphoma via PI3K/AKT pathway activation. *Leukemia,* **2012,** *26* (5), 1064-72.

[62] Dorsett, Y.; McBride, K.M.; Jankovic, M.; Gazumyan, A.; Thai, T. H.; Robbiani, D.F.; Di Virgilio, M.; Reina San-Martin, B.; Heidkamp, G.; Schwickert, T.A.; Eisenreich, T.; Rajewsky, K.; Nussenzweig, M. C. MicroRNA-155 suppresses activation-induced cytidine deaminase-mediated Myc-Igh translocation. *Immunity,* **2008,** *28* (5), 630-8.

[63] (a) Gao, P.; Tchernyshyov, I.; Chang, T.C.; Lee, Y.S.; Kita, K.; Ochi, T.; Zeller, K.I.; De Marzo, A.M.; Van Eyk, J.E.; Mendell, J. T.; Dang, C.V. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. *Nature,* **2009,** *458* (7239), 762-5; (b) Chang, T.C.; Yu, D.; Lee, Y.S.; Wentzel, E.A.; Arking, D.E.; West, K.M.; Dang, C.V.; Thomas-Tikhonenko, A.; Mendell, J.T. Widespread microRNA repression by Myc contributes to tumorigenesis. *Nat. Genet.,* **2008,** *40* (1), 43-50; (c) Bueno, M.J.; Gomez de Cedron, M.; Gomez-Lopez, G.; Perez de Castro, I.; Di Lisio, L.; Montes-Moreno, S.; Martinez, N.; Guerrero, M.; Sanchez-Martinez, R.; Santos, J.; Pisano, D.G.; Piris, M.A.; Fernandez-Piqueras, J.; Malumbres, M. Combinatorial effects of microRNAs to suppress the Myc oncogenic pathway. *Blood,* **2011,** *117* (23), 6255-66.

[64] Leucci, E.; Cocco, M.; Onnis, A.; De Falco, G.; van Cleef, P.; Bellan, C.; van Rijk, A.; Nyagol, J.; Byakika, B.; Lazzi, S.; Tosi, P.; van Krieken, H.; Leoncini, L. MYC translocation-negative classical Burkitt lymphoma cases: an alternative pathogenetic mecha-

nism involving miRNA deregulation. *J. Pathol.,* **2008,** *216* (4), 440-50.

[65] Tan, L.P.; Seinen, E.; Duns, G.; de Jong, D.; Sibon, O.C.; Poppema, S.; Kroesen, B.J.; Kok, K.; van den Berg, A. A high throughput experimental approach to identify miRNA targets in human cells. *Nucleic Acids Res.,* **2009,** *37* (20), e137.

[66] Navarro, A.; Diaz, T.; Martinez, A.; Gaya, A.; Pons, A.; Gel, B.; Codony, C.; Ferrer, G.; Martinez, C.; Montserrat, E.; Monzo, M. Regulation of JAK2 by miR-135a: prognostic impact in classic Hodgkin lymphoma. *Blood,* **2009,** *114* (14), 2945-51.

[67] Nie, K.; Gomez, M.; Landgraf, P.; Garcia, J.F.; Liu, Y.; Tan, L.H.; Chadburn, A.; Tuschl, T.; Knowles, D.M.; Tam, W. MicroRNA-mediated down-regulation of PRDM1/Blimp-1 in Hodgkin/Reed-Sternberg cells: a potential pathogenetic lesion in Hodgkin lymphomas. *Am. J. Pathol.,* **2008,** *173* (1), 242-52.

[68] Leucci, E.; Zriwil, A.; Gregersen, L.H.; Jensen, K.T.; Obad, S.; Bellan, C.; Leoncini, L.; Kauppinen, S.; Lund, A.H. Inhibition of miR-9 de-represses HuR and DICER1 and impairs Hodgkin lymphoma tumour outgrowth *in vivo*. *Oncogene,* **2012**, *31*(49), 5081-9.

[69] Craig, V.J.; Cogliatti, S.B.; Imig, J.; Renner, C.; Neuenschwander, S.; Rehrauer, H.; Schlapbach, R.; Dirnhofer, S.; Tzankov, A.; Muller, A. Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. *Blood,* **2011,** *117* (23), 6227-36.

[70] Craig, V.J.; Cogliatti, S.B.; Rehrauer, H.; Wundisch, T.; Muller, A. Epigenetic silencing of microRNA-203 dysregulates ABL1 expression and drives Helicobacter-associated gastric lymphomagenesis. *Cancer Res.,* **2011,** *71* (10), 3616-24.

[71] Thorns, C.; Kuba, J.; Bernard, V.; Senft, A.; Szymczak, S.; Feller, A.C.; Bernd, H.W. Deregulation of a distinct set of microRNAs is associated with transformation of gastritis into MALT lymphoma. *Virchows Arch.,* **2012,** *460* (4), 371-7.

[72] Liu, T.Y.; Chen, S.U.; Kuo, S.H.; Cheng, A.L.; Lin, C.W. E2A-positive gastric MALT lymphoma has weaker plasmacytoid infiltrates and stronger expression of the memory B-cell-associated miR-223: possible correlation with stage and treatment response. *Mod. Pathol.,* **2010,** *23* (11), 1507-17.

[73] Bouteloup, M.; Verney, A.; Rachinel, N.; Callet-Bauchu, E.; Ffrench, M.; Coiffier, B.; Magaud, J.P.; Berger, F.; Salles, G.A.; Traverse-Glehen, A. MicroRNA expression profile in splenic marginal zone lymphoma. *Br. J. Haematol.,* **2012,** *156* (2), 279-81.

[74] Ballabio, E.; Mitchell, T.; van Kester, M.S.; Taylor, S.; Dunlop, H. M.; Chi, J.; Tosi, I.; Vermeer, M.H.; Tramonti, D.; Saunders, N.J.; Boultwood, J.; Wainscoat, J.S.; Pezzella, F.; Whittaker, S.J.; Tensen, C.P.; Hatton, C.S.; Lawrie, C.H. MicroRNA expression in Sezary syndrome: identification, function, and diagnostic potential. *Blood,* **2010,** *116* (7), 1105-1113.

[75] (a) Qin, Y.; Buermans, H.P.; van Kester, M.S.; van der Fits, L.; Out-Luiting, J.J.; Osanto, S.; Willemze, R.; Vermeer, M.H.; Tensen, C.P. Deep-sequencing analysis reveals that the miR-199a2/214 cluster within DNM3os represents the vast majority of aberrantly expressed microRNAs in Sezary syndrome. *J. Invest. Dermatol.,* **2012,** *132* (5), 1520-2; (b) Narducci, M.G.; Arcelli, D.; Picchio, M.C.; Lazzeri, C.; Pagani, E.; Sampogna, F.; Scala, E.; Fadda, P.; Cristofoletti, C.; Facchiano, A.; Frontani, M.; Monopoli, A.; Ferracin, M.; Negrini, M.; Lombardo, G.A.; Caprini, E.; Russo, G. MicroRNA profiling reveals that miR-21, miR486 and miR-214 are upregulated and involved in cell survival in Sezary syndrome. *Cell Death Dis.,* **2011,** *2*, e151.

[76] Cristofoletti, C.; Picchio, M.C.; Lazzeri, C.; Tocco, V.; Pagani, E.; Bresin, A.; Mancini, B.; Passarelli, F.; Facchiano, A.; Scala, E.; Lombardo, G.A.; Cantonetti, M.; Caprini, E.; Russo, G.; Narducci, M.G. Comprehensive analysis of PTEN status in Sezary syndrome. *Blood,* **2013,** *122* (20), 3511-20.

[77] van Kester, M.S.; Ballabio, E.; Benner, M.F.; Chen, X.H.; Saunders, N.J.; van der Fits, L.; van Doorn, R.; Vermeer, M.H.; Willemze, R.; Tensen, C.P.; Lawrie, C.H. miRNA expression profiling of mycosis fungoides. *Mol. Oncol.,* **2011,** *5* (3), 273-80.

[78] Benner, M. F.; Ballabio, E.; van Kester, M. S.; Saunders, N. J.; Vermeer, M.H.; Willemze, R.; Lawrie, C.H.; Tensen, C.P. Primary cutaneous anaplastic large cell lymphoma shows a distinct miRNA expression profile and reveals differences from tumor-stage mycosis fungoides. *Exp. Dermatol.,* **2012,** *21* (8), 632-4.

[79] Ralfkiaer, U.; Hagedorn, P.H.; Bangsgaard, N.; Lovendorf, M.B.; Ahler, C.B.; Svensson, L.; Kopp, K.L.; Vennegaard, M.T.; Lauenborg, B.; Zibert, J.R.; Krejsgaard, T.; Bonefeld, C.M.; Sokilde, R.; Gjerdrum, L.M.; Labuda, T.; Mathiesen, A.M.; Gronbaek, K.; Wasik, M.A.; Sokolowska-Wojdylo, M.; Queille-Roussel, C.; Gniadecki, R.; Ralfkiaer, E.; Geisler, C.; Litman, T.; Woetmann, A.; Glue, C.; Ropke, M.A.; Skov, L.; Odum, N. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). *Blood,* **2011,** *118* (22), 5891-900.

[80] Bezman, N.A.; Chakraborty, T.; Bender, T.; Lanier, L.L. miR-150 regulates the development of NK and iNKT cells. *J. Exp. Med.,* **2011,** *208* (13), 2717-31.

[81] Ghisi, M.; Corradin, A.; Basso, K.; Frasson, C.; Serafin, V.; Mukherjee, S.; Mussolin, L.; Ruggero, K.; Bonanno, L.; Guffanti, A.; De Bellis, G.; Gerosa, G.; Stellin, G.; D'Agostino, D. M.; Basso, G.; Bronte, V.; Indraccolo, S.; Amadori, A.; Zanovello, P. Modulation of microRNA expression in human T-cell development: targeting of NOTCH3 by miR-150. *Blood,* **2011,** *117* (26), 7053-62.

[82] Manfe, V.; Biskup, E.; Rosbjerg, A.; Kamstrup, M.; Skov, A.G.; Lerche, C.M.; Lauenborg, B.T.; Odum, N.; Gniadecki, R. miR-122 regulates p53/Akt signalling and the chemotherapy-induced apoptosis in cutaneous T-cell lymphoma. *PLoS One,* **2012,** *7* (1), e29541.

[83] Calin, G.A.; Dumitru, C.D.; Shimizu, M.; Bichi, R.; Zupo, S.; Noch, E.; Aldler, H.; Rattan, S.; Keating, M.; Rai, K.; Rassenti, L.; Kipps, T.; Negrini, M.; Bullrich, F.; Croce, C.M. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc. Natl. Acad. Sci. USA,* **2002,** *99* (24), 15524-9.

[84] Takamizawa, J.; Konishi, H.; Yanagisawa, K.; Tomida, S.; Osada, H.; Endoh, H.; Harano, T.; Yatabe, Y.; Nagino, M.; Nimura, Y.; Mitsudomi, T.; Takahashi, T. Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Res.,* **2004,** *64* (11), 3753-6.

[85] Lu, J.; Getz, G.; Miska, E.A.; Alvarez-Saavedra, E.; Lamb, J.; Peck, D.; Sweet-Cordero, A.; Ebert, B.L.; Mak, R.H.; Ferrando, A. A.; Downing, J.R.; Jacks, T.; Horvitz, H.R.; Golub, T.R. MicroRNA expression profiles classify human cancers. *Nature,* **2005,** *435* (7043), 834-8.

[86] Swerdlow, S.; Campo, E.; Harris, N. L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J.; Vardiman, J.W. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue (4th ed.)*. International Agency for Research on Cancer: **2008**.

[87] Connors, J.M. Non-Hodgkin lymphoma: the clinician's perspective--a view from the receiving end. *Mod. Pathol.,* **2013,** *26 Suppl 1*, S111-8.

[88] Lenz, G.; Davis, R.E.; Ngo, V.N.; Lam, L.; George, T.C.; Wright, G.W.; Dave, S.S.; Zhao, H.; Xu, W.; Rosenwald, A.; Ott, G.; Muller-Hermelink, H.K.; Gascoyne, R.D.; Connors, J.M.; Rimsza, L.M.; Campo, E.; Jaffe, E.S.; Delabie, J.; Smeland, E.B.; Fisher, R. I.; Chan, W.C.; Staudt, L.M. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. *Science,* **2008,** *319* (5870), 1676-9.

[89] Lawrie, C.H.; Larrea, E.; Larrinaga, G.; Goicoechea, I.; Cáceres, F.; Arestin, M.; Fernandez-Mercado, M.; Manterola, L.; López, J.I. Targeted next generation sequencing and non-coding RNA expression analysis of clear cell papillary renal cell carcinoma suggests distinct pathological mechanisms from other renal tumour subtypes. *J. Pathol., J. Pathol.,* **2014**, 232 (1), 32-42.

[90] (a) Pathak, A.K.; Bhutani, M.; Kumar, S.; Mohan, A.; Guleria, R. Circulating cell-free DNA in plasma/serum of lung cancer patients as a potential screening and prognostic tool. *Clin. Chem.,* **2006,** *52* (10), 1833-42; (b) Anker, P.; Mulcahy, H.; Stroun, M. Circulating nucleic acids in plasma and serum as a noninvasive investigation for cancer: time for large-scale clinical studies? *Int. J. Cancer,* **2003,** *103* (2), 149-52.

[91] Duttagupta, R.; Jiang, R.; Gollub, J.; Getts, R.C.; Jones, K.W. Impact of Cellular miRNAs on Circulating miRNA Biomarker Signatures. *PLoS ONE,* **2011**, *6* (6), e20769.

[92] Mitchell, P.S.; Parkin, R.K.; Kroh, E.M.; Fritz, B.R.; Wyman, S.K.; Pogosova-Agadjanyan, E.L.; Peterson, A.; Noteboom, J.; O'Briant, K.C.; Allen, A.; Lin, D.W.; Urban, N.; Drescher, C.W.; Knudsen, B.S.; Stirewalt, D.L.; Gentleman, R.; Vessella, R.L.; Nelson, P.S.; Martin, D.B.; Tewari, M. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc. Natl. Acad. Sci. USA,* **2008,** *105* (30), 10513-8.

[93] Lawrie, C.H. MicroRNA expression in lymphoma. *Expert Opin. Biol. Therapy,* **2007,** *7* (9), 1363-74.

[94] Lawrie, C.H.; Gal, S.; Dunlop, H.M.; Pushkaran, B.; Liggins, A. P.;

Pulford, K.; Banham, A.H.; Pezzella, F.; Boultwood, J.; Wainscoat, J.S.; Hatton, C.S.; Harris, A.L. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br. J. Haematol.,* **2008,** *141* (5), 672-5.

[95] Chen, W.; Wang, H.; Chen, H.; Liu, S.; Lu, H.; Kong, D.; Huang, X.; Kong, Q.; Lu, Z. Clinical significance and detection of microRNA-21 in serum of patients with diffuse large B-cell lymphoma in Chinese population. *Eur. J. Haematol.,* **2014**, *92* (5), 407-12.

[96] Fang, C.; Zhu, D.X.; Dong, H.J.; Zhou, Z.J.; Wang, Y.H.; Liu, L.; Fan, L.; Miao, K. R.; Liu, P.; Xu, W.; Li, J.Y. Serum microRNAs are promising novel biomarkers for diffuse large B cell lymphoma. *Ann. Hematol.,* **2012,** *91* (4), 553-9.

[97] Ohyashiki, K.; Umezu, T.; Yoshizawa, S.; Ito, Y.; Ohyashiki, M.; Kawashima, H.; Tanaka, M.; Kuroda, M.; Ohyashiki, J.H. Clinical impact of down-regulated plasma miR-92a levels in non-Hodgkin's lymphoma. *PLoS One,* **2011,** *6* (2), e16408.

[98] (a) Yoshizawa, S.; Ohyashiki, J.H.; Ohyashiki, M.; Umezu, T.; Suzuki, K.; Inagaki, A.; Iida, S.; Ohyashiki, K. Downregulated plasma miR-92a levels have clinical impact on multiple myeloma and related disorders. *Blood Cancer J.,* **2012,** *2* (1), e53; (b) Tanaka, M.; Oikawa, K.; Takanashi, M.; Kudo, M.; Ohyashiki, J.; Ohyashiki, K.; Kuroda, M. Down-regulation of miR-92 in human plasma is a novel marker for acute leukemia patients. *PloS One,* **2009,** *4* (5), e5532.

[99] Jones, K.; Nourse, J.P.; Keane, C.; Bhatnagar, A.; Gandhi, M.K. Plasma microRNA are disease response biomarkers in classical Hodgkin lymphoma. *Clin. Cancer Res.,* **2014,** *20* (1), 253-64.

[100] Guo, H.Q.; Huang, G.L.; Guo, C.C.; Pu, X.X.; Lin, T.Y. Diagnostic and prognostic value of circulating miR-221 for extranodal natural killer/T-cell lymphoma. *Dis. Markers,* **2010,** *29* (5), 251-8.

[101] Alencar, A.J.; Malumbres, R.; Kozloski, G.A.; Advani, R.; Talreja, N.; Chinichian, S.; Briones, J.; Natkunam, Y.; Sehn, L.H.; Gascoyne, R.D.; Tibshirani, R.; Lossos, I.S. MicroRNAs are independent predictors of outcome in diffuse large B-cell lymphoma patients treated with R-CHOP. *Clin. Cancer Res.,* **2011,** *17* (12), 4125-35.

[102] Iqbal, J.; Shen, Y.; Huang, X.; Liu, Y.; Wake, L.; Liu, C.; Deffenbacher, K.; Lachel, C.M.; Wang, C.; Rohr, J.; Guo, S.; Smith, L. M.; Wright, G.; Bhagavathi, S.; Dybkaer, K.; Fu, K.; Greiner, T. C.; Vose, J.M.; Jaffe, E.; Rimsza, L.; Rosenwald, A.; Ott, G.; Delabie, J.; Campo, E.; Braziel, R.M.; Cook, J.R.; Tubbs, R.R.; Armitage, J.O.; Weisenburger, D.D.; Staudt, L.M.; Gascoyne, R.D.; McKeithan, T.W.; Chan, W.C. Global microRNA expression profiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma. *Blood,* **2015,** *125* (7), 1137-45.

[103] Bui, T.V.; Mendell, J.T. Myc: Maestro of MicroRNAs. *Genes Cancer,* **2010,** *1* (6), 568-575.

[104] (a) Di Martino, M.T.; Leone, E.; Amodio, N.; Foresta, U.; Lionetti, M.; Pitari, M.R.; Cantafio, M.E.; Gulla, A.; Conforti, F.; Morelli, E.; Tomaino, V.; Rossi, M.; Negrini, M.; Ferrarini, M.; Caraglia, M.; Shammas, M.A.; Munshi, N.C.; Anderson, K.C.; Neri, A.; Tagliaferri, P.; Tassone, P. Synthetic miR-34a mimics as a novel therapeutic agent for multiple myeloma: *in vitro* and *in vivo* evidence. *Clin. Cancer Res.,* **2012,** *18* (22), 6260-70; (b) Medina, P.P.; Nolde, M.; Slack, F.J. OncomiR addiction in an *in vivo* model of microRNA-21-induced pre-B-cell lymphoma. *Nature,* **2010,** *467* (7311), 86-90.

[105] Akinc, A.; Zumbuehl, A.; Goldberg, M.; Leshchiner, E.S.; Busini, V.; Hossain, N.; Bacallado, S.A.; Nguyen, D.N.; Fuller, J.; Alvarez, R.; Borodovsky, A.; Borland, T.; Constien, R.; de Fougerolles, A.; Dorkin, J.R.; Narayanannair Jayaprakash, K.; Jayaraman, M.; John, M.; Koteliansky, V.; Manoharan, M.; Nechev, L.; Qin, J.; Racie, T.; Raitcheva, D.; Rajeev, K.G.; Sah, D.W.; Soutschek, J.; Toudjarska, I.; Vornlocher, H.P.; Zimmermann, T.S.; Langer, R.; Anderson, D.G. A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. *Nat. Biotechnol.,* **2008,** *26* (5), 561-9.

[106] Chen, W.; Wang, H.; Chen, H.; Liu, S.; Lu, H.; Kong, D.; Huang, X.; Kong, Q.; Lu, Z. Clinical significance and detection of microRNA-21 in serum of patients with diffuse large B-cell lymphoma in Chinese population. *Eur. J. Haematol.,* **2014,** *92* (5), 407-12.

[107] Knudsen, S.; Hother, C.; Gronbaek, K.; Jensen, T.; Hansen, A.; Mazin, W.; Dahlgaard, J.; Moller, M.B.; Ralfkiaer, E.; Brown Pde, N. Development and Blind Clinical Validation of a MicroRNA Based Predictor of Response to Treatment with R-CHO(E)P in DLBCL. *PLoS One,* **2015,** *10* (2), e0115538.

[108] Sanchez-Espiridion, B.; Martin-Moreno, A.M.; Montalban, C.; Figueroa, V.; Vega, F.; Younes, A.; Medeiros, L.J.; Alves, F.J.; Canales, M.; Estevez, M.; Menarguez, J.; Sabin, P.; Ruiz-Marcellan, M.C.; Lopez, A.; Sanchez-Godoy, P.; Burgos, F.; Santonja, C.; Lopez, J.L.; Piris, M.A.; Garcia, J.F. MicroRNA signatures and treatment response in patients with advanced classical Hodgkin lymphoma. *Br. J. Haematol.,* **2013,** *162* (3), 336-47.

[109] Ballabio, E.; Mitchell, T.; van Kester, M.S.; Taylor, S.; Dunlop, H.M.; Chi, J.; Tosi, I.; Vermeer, M.H.; Tramonti, D.; Saunders, N.J.; Boultwood, J.; Wainscoat, J.S.; Pezzella, F.; Whittaker, S.J.; Tensen, C.P.; Hatton, C.S.; Lawrie, C.H. MicroRNA expression in Sezary syndrome: identification, function, and diagnostic potential. *Blood,* **2010,** *116* (7), 1105-13.

Received on: April 01, 2015 **Revised on: April 20, 2015** **Accepted on: April 22, 2015**