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Review

miRNA-Based Therapies in B Cell Non-Hodgkin Lymphoma

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Non-Hodgkin lymphoma (NHL) is a diverse class of hematological cancers, many of which arise from germinal center (GC)-experienced B cells. Thus GCs, the sites of antibody affinity maturation triggered during immune responses, also provide an environment that facilitates B cell oncogenic transformation. miRNAs provide attractive and mechanistically different strategies to treat these malignancies based on their potential for simultaneous modulation of multiple targets. Here, we discuss the scientific rationale for miRNA-based therapeutics in B cell neoplasias and review recent advances that may help establish a basis for novel candidate miRNA-based therapies for B cell-NHL (B-NHL).

miRNA-Based Therapies in B-NHL

Lymphomas arise from the neoplastic transformation of either T or B lymphocytes. About 95% of all human lymphomas originate in B cells, rather than T cells, and most of them (75–85%) arise from mature B cells that are **germinal center** (**GC**, see Glossary) experienced [1]. GCs are unique structures in which Ig genes are remodeled and are thus essential for the generation of high-affinity antibodies required for a proficient immune response. The production of high-affinity antibodies entails the introduction of mutations and DNA double-strand breaks in Ig genes and thus increases the risk of generating oncogenic events in mature B cells that transit through the GC [2,3]. Mature B cell neoplasia underlies the vast majority of lymphocyte-derived cancers, including most B-NHLs, such as diffuse large B cell lymphomas (DLBCLs), follicular lymphoma (FL), Burkitt lymphoma (BL), multiple myeloma (MM), and B cell chronic lymphocytic leukemia (CLL) [4]. It is estimated that B-NHL affects 1.3 million people worldwide [Global Cancer Observatory (GCO), World Health Organization[i]].

While some types of B-NHL progress relatively slowly and are considered indolent cancers, about 60% of them, including BL and DLBCL, are aggressive and require immediate intervention [1]. In general, the main treatments for mature B-NHL are chemotherapy, immunochemotherapy, and radiation therapy; however, a significant fraction of these cancers are refractory to these interventions or relapse after treatment [1,5]. There is therefore an urgent need for alternative therapeutic strategies to replace or complement current approaches. Advances in knowledge of the molecular mechanisms underlying lymphomagenesis have led to the design of promising new drugs that target specific genes and proteins involved in neoplasia development or maintenance. Clinically available strategies targeting B-NHL currently include: (i) immunotherapy with cell-directed monoclonal antibodies and **chimeric antigen receptor (CAR) T cell therapy**; and (ii) signal transduction inhibitors, including proteasome inhibitors, histone deacetylase (HDAC) inhibitors, and B cell receptor (BCR) signaling kinase inhibitors [6]. The availability of targeted therapies has improved treatment options for certain B cell neoplasias in some patients. However, current targeted therapies have important limitations; most notably, treatment failure due to the selective pressure to generate drug-resistant mutations in tumor cells [5]. In recent years, miRNAs have emerged as new therapeutic tools for mature B cell malignancies due to their unique molecular features, as described below.

Highlights

Modulation of the expression of the oncomiRs miR-17-92, miR-21, and miR-155 and the tumor suppressor miRNAs miR-144/451, miR-181a, miR-27, miR-28-5p, and miR-34a has shown therapeutic potential in xenograft mouse models of human B-cell non-Hodgkin lymphoma (B-NHL) *in vivo*.

Changing the expression of various miRNAs can increase sensitivity to R-CHOP chemotherapy components and B-NHL-targeted drugs such as bortezomib and imatinib in certain B-NHLs.

Several miRNAs have been identified as regulators of the expression of the inhibitory receptor programmed cell death-1 (PD-1) and its ligand PD-L1. Shifting the expression of these miRNAs might contribute to the improvement of immunotherapy-based B-NHL treatments.

miRNA expression patterns might be used as putative biomarkers for certain B-NHLs to predict survival, relapse, remission, and responsiveness to specific treatments.

MRX34 (miR-34 mimic), mesomiR-1 (miR-16 mimic), and cobomarsen (anti-miR-155) have shown antitumor activity in Phase I clinical trials. Although not specifically designed for B-NHL, these trials included B-NHL patients.

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A high proportion of human miRNAs are located in cancer-associated genomic regions, and dysregulated miRNA expression is a hallmark of most cancers, including lymphomas [7]. In B cell neoplasia, miRNAs can function both as oncogenes (**oncomiRs**) and as tumor suppressor genes (reviewed in [8]), and the possibility of delivering synthetic **miRNA mimics** or miRNA inhibitors to manipulate miRNA expression *in vivo* has opened new and exciting therapeutic perspectives [9]. Notably, the ability of miRNAs to target multiple protein-coding genes in the same pathways is expected to limit the generation of drug resistance [10–12].

Here, we review the oncogenic and tumor suppressor actions of miRNAs in B-NHL, with particular emphasis on *in vivo* studies addressing the therapeutic potential of miRNA modulation. We also discuss studies exploring miRNA-based combination strategies to treat B cell neoplasias and the use of miRNAs as putative biomarkers to track responses to novel treatments for B cell malignancies, describing ongoing miRNA-based clinical trials for specific cancers (Figure 1, Key Figure). Finally, we comment on the current challenges and future directions of this exciting and promising field.

miRNAs

miRNAs are noncoding RNAs (ncRNAs) that drive post-transcriptional negative regulation of gene expression by promoting the degradation or translational blockade of their target mRNAs. miRNAs are 21–24-nucleotide-long RNA molecules that are processed from longer RNA precursors (pri-miRNAs) [13], and either the 5′ or the 3′ strand of the mature miRNA duplex is loaded into the Argonaute (AGO) family of proteins to form a miRNA-induced silencing complex (miRISC) [13]. When bound to AGO proteins, mature miRNAs destabilize or inhibit the translation of partially

Key Figure

miRNA Expression Deregulation Is a Common Feature of B Cell Non-Hodgkin Lymphoma (B-NHL)

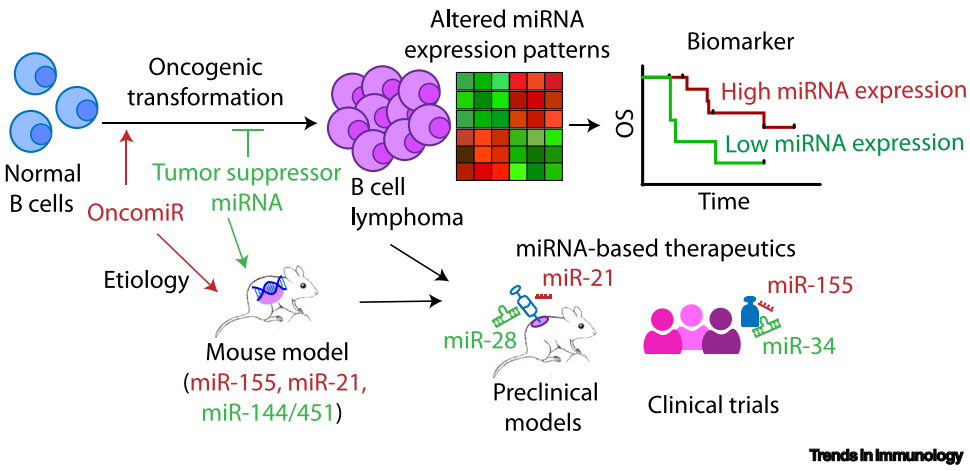


Figure 1. miRNAs have been shown to function both as oncogenes (oncomiRs; e.g., miR-155, miR-21; in red) and as tumor suppressor genes (e.g., miR-144/451; in green) for B-NHL development using genetically modified mouse models. Altered miRNA expression patterns in B-NHL samples might be used as prognostic and/or predictive biomarkers of disease. miRNA-based clinical applications are being developed first using mouse preclinical models based on miRNA modulation (e.g., miR-21 inhibition, miR-28 restoration) and in subsequent clinical trials in cancer patients (including miR-155 inhibition or miR-34 restoration). Abbreviation: OS, overall survival.

Glossary

λ-*MYC* transgenic: B cell-specific *MYC* transgenic mouse model that overexpresses the *MYC* oncogene under the control of the Ig lambda (Igλ) light chain and recapitulates pathogenic features of human BL lymphoma.
Anti-miR: synthetic chemically modified RNA nucleotide complementary to the mature target miRNA.
Chimeric antigen receptor (CAR) T cell therapy: therapy based on the engineering of patient T cells to express a CAR that recognizes an antigen on targeted tumor cells.
Circular RNA: type of noncoding single-stranded RNA that forms a covalently closed continuous loop.
Conditional tet-off miR-21 mouse model: here, Cre/loxP and tetracycline-dependent gene expression of miR-21 at the *Rosa26* locus mouse model in which doxycycline silences the mir-21 gene.
DNA damage pathways: network of cellular responses that sense and repair DNA lesions to prevent the generation of deleterious mutations.
Eμ-*MYC* transgenic mice: B cells carry a *c-MYC* oncogene under the Ig heavy-chain enhancer (Eμ); mice develop B cell lymphomas by 4–6 months of age.
Eμ/VH miR-155 transgenic mice: expression of mmu-miR15 is under the control of a V_H promoter-Ig heavy chain Eμ enhancer, which becomes active at the late pro-B cell stage of B cell development.
Exosome: membrane-bound extracellular vesicles produced in the endosomal compartment of most eukaryotic cells; they play a role in intercellular communication by carrying signaling and regulatory elements, including miRNAs, from the cells of origin to target cells.
Germinal center (GC): site of secondary antibody diversification during immune responses in secondary lymphoid organs.
Immune-checkpoint inhibitors: drugs that act by releasing a natural 'brake' on effector cells of the immune system (e.g., T lymphocytes).
Liposomes: delivery system comprising a lipid bilayer and an internal aqueous phase; used to load and deliver cargoes such as chemotherapy drugs and nucleic acids to tumors.

complementary target mRNAs [13]. Animal miRNAs promote subtle changes in gene expression through imperfect pairing with their target mRNAs. Each miRNA can bind numerous different target mRNAs and can act as a regulator of gene networks rather than of individual genes (reviewed in [14–16]). However, genetic studies involving mutation of miRNA-binding sites in individual target genes have identified key target genes, demonstrating that individual miRNA–target mRNA interactions can play important roles in a cell- and context-dependent manner [17–20]. miRNA-mediated post-transcriptional regulation of gene expression is cell-type specific [21], is influenced by the relative abundance of mRNA targets in the cell, and can be balanced by other ncRNAs such as **circular RNAs** and **long-ncRNAs**, which have been described to function as **miRNA sponges** [22,23]. miRNAs can also regulate gene expression in a paracrine manner through transfer in **exosomes** to neighboring or synaptically linked cells [24]. Recent work demonstrated the key role of exosomal miRNA transfer in the regulation of GC responses [25] and in intercellular communication in solid-tumor microenvironments [26] in mice.

Oncogenic or Tumor Suppressor miRNAs in B Cell Neoplasia

Since the oncogenic potential of miRNAs for B cell lymphoma development was first reported in 2005 [27], numerous studies have advanced our understanding of the molecular mechanisms underlying the roles of miRNA in B cell transformation. Here, we cover representative miRNAs for which the therapeutic potential of miRNA modulation has been established in *in vivo* preclinical models. These studies are summarized in Table 1, together with other studies that have established a role for miRNAs in B cell neoplasias *in vivo* but these are not discussed here.

Oncogenic miRNAs

The miR-17~92 polycistron is an miRNA cluster whose expression is frequently elevated in human cancers [28]. The term 'oncomiR' was coined in a pioneering study showing that forced miR-17~92 expression in hematopoietic stem cells from **Eμ-myc transgenic mice** accelerated the generation of **preB cell lymphomas** [27,29]. Subsequent mouse studies revealed that the expression of miR-17~92 in B lymphocytes driven by *Cd19* or Ig heavy-chain promoters was sufficient to generate highly penetrant mature GC-derived B cell lymphomas [30,31]. The miR-17~92 cluster encodes six distinct miRNAs that are processed from a common primary transcript, and the key oncogenic component of the cluster was identified as miR-19 [32,33]. The miR-17~92 cluster regulates the expression of the tumor suppressors *Pten* and *P21* [34,35], the proapoptosis factors *Bim* [34] and *c-Myc* [36,37], and other key B cell survival and signaling pathways in mice (Table 1). The use of an interfering long-ncRNA to simultaneously inhibit 13 oncomiRs, including five miR-17~92 cluster miRNAs, was shown to inhibit human SUDHL-4 DLBCL xenograft growth [38]. These data revealed the potential of simultaneous targeting of multiple oncomiRs as a possible therapeutic strategy for B-NHL.

miR-21 is one of the most frequently upregulated miRNAs in human solid tumors and B-NHLs [39], and high miR-21 expression is associated with the activated B cell (ABC) subtype of DLBCL [40] in addition to low DLBCL patient survival [41]. In a brain- and hematopoietic system-specific **conditional tet-off miR-21 mouse model** driven by a NesCre8 Nestin Cre recombinase, miR-21 expression induced clonal and transplantable preB lymphomas [42]. The key finding of the study was that the lymphomas were dependent on miR-21 expression, because doxycycline-driven miR-21 removal triggered massive tumor regression due to apoptosis compared with non-doxycycline-treated controls [42]. Subsequent analysis demonstrated the therapeutic potential of synthetic miR-21 inhibitors in a non-miR-21-induced human OPM-2 xenograft model of multiple myeloma [43].

Long-ncRNAs: type of noncoding RNA with lengths exceeding 200 nucleotides; involved in chromatin remodeling, as well as transcriptional and post-transcriptional regulation.
Micelles: spherical and supermolecular nanoconstructs with a core-shell structure comprising both lipophilic and hydrophilic modules; able to either accommodate hydrophobic drugs internally or to incorporate small RNA molecules as external branches.
miR-155^{LSLtTA} conditional knock-in mouse model: bears Cre/loxP and tetracycline-dependent gene expression at the *Rosa26* locus; with doxycycline, this silences the expression of miR-155.
miRNA mimic: synthetic RNA oligonucleotide analog of a miRNA molecule.
miRNA sponges: synthetic constructs containing complementary sequences of a miRNA, cloned in tandem within the 3′UTR of a gene; function as competitive inhibitors for that miRNA.
Non-Hodgkin lymphoma (NHL): group of cancers of the lymphatic system. The vast majority of NHLs are mature B cell neoplasias.
OncomiR: miRNA whose expression induces oncogenic transformation.
Patient-derived xenografts (PDXs): preclinical models of cancer in which cells from a patient tumor are implanted into an immunodeficient mouse, aiming to accurately replicate the tumor cell growth, tumor cell diversity, and tumor progression of the original tumor, including metastatic potential.
preB cell lymphoma: precursor B cell lymphoma is a neoplasia of immature B lymphocytes.
R-CHOP: immunochemotherapy used to treat NHL; includes four drugs known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and the monoclonal antibody rituximab.
Synthetic 3D polymeric scaffolds: 3D polymeric matrix used to model the physiological growth of cancer cells.

Table 1. miRNAs in B Cell Neoplasias[a]

miRNA	Expression in B cell neoplasia	Effect of miRNA modulation on B cell neoplasia development	miRNA target in B lymphocytes and B cell lymphoma	Therapy potential in B-NHL
miR-17~92 polycistron (miR-17, miR-18a, miR-19a, miR-20a, miR-19b, and miR-92a) OncomiR	Increased expression in primary human B-NHL [27] due to gene amplifications [111] and *Myc*-mediated transcriptional upregulation [112,113]	Accelerates preB lymphoma development in Eμ-*MYC* transgenic mice [27] Induces GC-derived lymphomas in WT-background mice [30]	Inhibits expression of *Pten*, *P21* [34,35], *Bim* [34], and *c-Myc* [36,37] in mice Regulates cell survival and proliferation [30–32,114], apoptosis inhibition [115], chromatin regulation [115], BCR signaling amplification [116,117], and tumor metabolism [118] in human and mouse B cells	Simultaneous inhibition of 13 oncomiRs[b] limits human SUDHL-4 DLBCL xenograft growth [38] [b]Includes miR-21, miR-155, miR-221/222, miR-125a-5p/125b, and miR-146a/146b-5p as well as the miR-17-92 family members miR-17, miR-19a/19b, and miR-20a/20b
miR-19b OncomiR	Increased expression in primary human B-NHL [27] due to gene amplifications [111] and *Myc*-mediated transcriptional upregulation [112,113]	Accelerates preB lymphoma development in *MYC* transgenic mice [36,37] Expression is required for *c-Myc*-induced mouse lymphomagenesis [33]	Inhibits expression of *Pten*, *Bcl7a*, *Rnf42*, and *Sbf2* [32,33] in mouse B cells	NA
miR-21 OncomiR	Upregulated expression in primary human B-NHL [39], increased expression in ABC-DLBCL [40], expression associated with low DLBCL survival [41]	miR-21 induces preB lymphomas that are dependent on continuous miR-21 expression in mice [42]	Inhibits expression of *PTEN*, *PDCD4* [119], and *FOXO* [41] in human B-NHL cell lines Activates the PI3K–AKT–mTOR pathway and resistance to chemotherapy in CRL2631 human DLBCL cell line [41]	Synthetic miR-21 inhibitors impair human OPM-2 MM xenograft growth [43]
miR-155 OncomiR	Increased expression in primary human B-NHLs [44,45]	miR-155 induces preB and mature B cell lymphomas [46–49] in mice	Inhibits expression of *Spi1* [120], *Aicda* [17,18], *Ship1*, *Bcl6*, *Smad2*, *Smad5*, *Ctla4* [121], *Actr10*, *Hif1a*, *Jarid2*, and *Terf1* [21] in mouse B cells	miR-155 inhibition impairs the growth of B-NHL human cell-line xenografts [50,51] and primary mouse B cell lymphomas [49,52]
miR-217 OncomiR	DNA amplifications in human DLBCL [122] and increased expression in human B-NHL [123]	Overexpression in B cells leads to clonal GC-derived lymphomas in mice [123]	Downregulation of DNA damage and repair response through *Nbs1*, *Xrcc2*, *Lig4*, and *Pds5b* downregulation and *Bcl6* stabilization in mouse primary GC B cells [123]	NA
miR-181a Tumor suppressor	Downregulated expression in primary human ABC-DLBCL [55]	NA	NF-κB signaling [55] and *CARD11* [58] in human B HNL cell lines	miR-181a slows tumor growth rate in human OCILY10 and U2932 ABC-like DLBCL xenograft models [58,63]
miR-144/451 gene locus Tumor suppressor	Reduced expression of miR-144 and miR-451 in primary mouse *Myc*-driven B lymphomas and in highly expressing MYC human DLBCL [53]; reduced expression of miR-144 in highly expressing BCL-6 human primary BL, DLBCL, and FL and in cell lines [54]	Depletion of miR-144/451 locus accelerates B lymphoma generation in aged mice [53]	miR-451 directly represses *Myc* [53]; miR-144 directly represses *Bcl6* [54] in mice	Transduction of miR-144 and miR-451 inhibits mouse *Myc3* and human Daudi B cell line lymphoma growth [53]; miR-144 overexpression inhibits OCI-Ly3 DLBCL xenograft growth [54]
miR-27b Tumor suppressor	Downregulated expression associated with poor prognosis in human DLBCL [56]; low expression in human SMZL [57]	NA	miR-27 directly represses the proto-oncogene *MET* and inhibits MET–PI3K–AKT pathway activity in human NHL cell lines [56]	Transduction of miR-27 inhibits OCI-LY8 human DLBCL xenograft growth [56]
miR-34a Tumor suppressor	Lost or low expression in numerous human primary B-NHLs; low expression is associated with poor prognosis	No direct evidence; deletion of miR-34 does not accelerate *Myc*-induced lymphomas in mice [73]	miR-34 inhibits direct transcriptional targets of *P53* that regulate the cell cycle, the DNA damage response [65],	Intratumor or systemic administration of miR-34a synthetic mimics efficiently inhibits 2932 ABC-DLBCL and

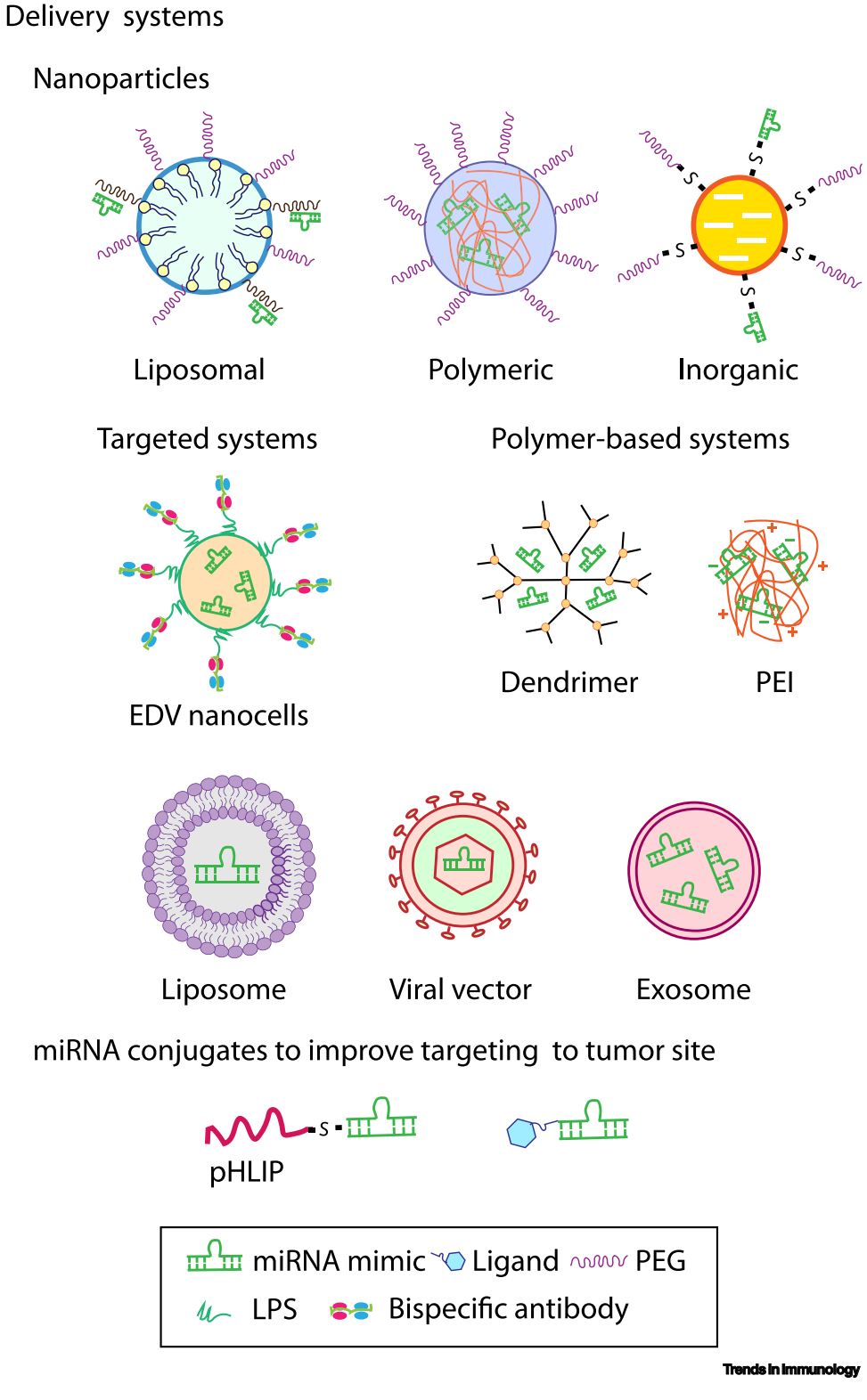
(continued on next page)

Table 1. (continued)

miRNA	Expression in B cell neoplasia	Effect of miRNA modulation on B cell neoplasia development	miRNA target in B lymphocytes and B cell lymphoma	Therapy potential in B-NHL
	in CLL, DLBCL, MCL, and MALT lymphoma [72]; epigenetic inactivation of miR-34a in B-NHL [71]		apoptosis [66], and the expression of *FOXP1* [67], *BMYB* [68], *C-MYC* [69], *BCL2*, *CDK6*, and *NOTCH1* [70] in human and mouse B cells	SKMM1 MM xenograft growth [66,70]; inhibition of primary human MM growth in SCID-synth-hum mouse model with miR-34a mimics [70]
miR-28 Tumor suppressor	Lost or low expression in numerous human primary B-NHLs [59–62]; low expression is associated with poor prognosis in DLBCL [63]; loss of miR-28 in B-NHL due to epigenetic inactivation [61], genomic deletions [124], and *Myc* transcriptional regulation [60]	NA	BCR signaling, proliferation, and apoptosis through the downregulation of *MAD2L1*, *BAG1*, *RAP1B*, *BLC2*, *NFKB2*, and *p-AKT* in human B-NHL cell lines [59,60]	Efficient inhibition of tumor growth after intratumor or systemic administration of miR-28 synthetic mimics in human MD901 DLBCL and Ramos BL cell line xenograft models and in a primary mouse BL [59]
miR-145 Tumor suppressor	Reduced expression in plasma from primary human MM and in human MM cell lines [125]	NA	miR-145 inhibits survival by targeting *BIRC5* and *BCL2* [125]; miR-145-3p targets HDAC4 [97] human MM B cell lines	miR-145 mimics inhibit H929 MM xenograft growth [125] and miR-145-3p enhances human LP-1 MM cell line sensitivity to bortezomib [97]
miR-146a and miR-146b Tumor suppressors	Reduced expression of miR-146b in human primary DLCBL [126]; low expression predicts poor treatment response in DLBCL patients [127]	miR-146a KO mice spontaneously develop B lymphomas and myeloid malignancies [128]; miR-146b and miR-146a KO mice develop histologically different B cell lymphoma [129]; miR-146a deficiency accelerates *c-Myc*-induced B cell lymphomas in mice [130]	miR-146a and miR-146b inhibit NF-κB-mediated transcription through *Traf6* and *Irak1* downregulation [128,129]; miR-146a downregulates *Egr1* [130] in mouse B cells	NA for B cell neoplasia; targeted delivery of synthetic miR-146a inhibits progression of human MDS and AML leukemic cell lines in xenograft models [107]

[a]Abbreviations: KO, knockout; ; MALT, extranodal marginal zone lymphoma; MDS, myelodysplastic syndrome; NA, not assessed.

One of the most extensively studied oncomiRs is miR-155, with numerous reports on its therapeutic potential to inhibit B cell neoplasias. Specifically, miR-155 expression is increased in several lymphoid malignancies, including CLL and DLBCL [44,45]; moreover, the expression of miR-155 is oncogenic in B cell-specific **Eμ/VH miR-155 transgenic mice**, which develop transplantable acute lymphoblastic leukemia (ALL)/high-grade lymphomas [46–48]. Later studies using the **miR-155^{LSLtTA} conditional knock-in mouse model** revealed that miR-155-induced preB clonal and transplantable lymphomas were dependent on continuous miR-155 expression, such that miR-155 withdrawal caused rapid tumor regression [49]. Synthetic miR-155 inhibitors have shown promising therapeutic potential both in mCherry-Luc-BCWM1 and OCI-Ly3 B-NHL cell line xenograft models [50,51] and in miR-155-induced primary B cell lymphomas [49,52]. In the latter, miR-155 was inhibited using optimized **anti-miR** delivery techniques, such as the loading of peptide nucleic acid anti-miR-155 conjugates in biodegradable polymer nanoparticles covered with a cell-penetrating peptide, resulting in reduced tumor volume growth [49]. In a different study, miR-155 was inhibited by attaching anti-miR-155 to a low-pH-induced transmembrane structure (pHLIP) targeting the tumor microenvironment (Figure 2); this resulted in efficient inhibition of tumor growth and increased mouse survival relative to controls [52]. Thus, based on miR-155 expression patterns in human B cell neoplasias, *in vivo* functional studies, and preclinical assays, miR-155 represents a strong candidate therapeutic target, which certainly merits further robust testing.



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Tumor Suppressor miRNAs

The role and therapeutic potential of a set of tumor suppressor miRNAs whose expression is lost or reduced in B cell neoplasias has been studied using mainly human B lymphoma cell line xenograft mouse models. Restoration of tumor suppressor miRNA expression has been achieved through viral modification or by administering clinically amenable synthetic miRNA mimics (Figure 2).

miR-144/451 is a bicistronic tumor suppressor miRNA locus, and miR-144/451$^{-/-}$ aged mice have shown an increased frequency of spontaneous B lymphoma generation compared with wild-type (WT) mice [53]. Specifically, gain- and loss-of function assays combined with miRNA–3′UTR interaction luciferase reporter assays, showed that miR-451a and miR-144 inhibited *Myc* and *Bcl6* expression, respectively, in B lymphocytes [53,54]. In a regulatory loop, miR-144/451 were in turn negatively regulated by *Myc* [53] and *Bcl6* [54], two prominent B cell proto-oncogenes. miR-144/451 were also reported to contribute to B cell lymphomagenesis in xenograft mouse models by promoting the expression of these two proto-oncogenes. [53,54]. In agreement with these data, restoration of miR-144 and miR-451 expression through virus-mediated delivery was shown to inhibit OCI-Ly3, Myc3, and Daudi B cell-line xenograft growth *in vivo* in mice [53,54], providing a formal proof of their tumor suppressor activity in certain B cell lymphomas.

Similarly, miR-181a (whose expression is downregulated in human ABC versus GC DLBCL) [55] and miR-27b [downregulated in human DLBCL and splenic marginal zone lymphoma (SMZL) and associated with poor prognosis in DLBCL] [56,57] have been shown to inhibit human OCI-LY6, OCI-LY10, and OCI-LY19 DLBCL cell-line xenograft growth after virus-mediated miRNA restoration [55,56,58].

miR-28a-5p is an miRNA that negatively regulates the GC reaction in mice [59] and whose expression is reduced in numerous human B cell neoplasias [59–63]. miR-28 a-5p inhibits human P3HR1 and Raji B cell proliferation and promotes cellular apoptosis *in vitro* [60]. Furthermore, combined transcriptome and proteomic profiling in human Ramos BL cells have revealed that miR-28a-5p can downregulate downstream BCR signaling effectors, such as *PI3K* and *AKT*, that play key roles in human and mouse B lymphocyte proliferation and survival [4] and whose expression is frequently upregulated in GC-derived malignancies [4]. Our group has shown that intratumor or systemic administration of synthetic miR-28a-5p mimics in **liposomes** (Figure 2) inhibits tumor growth in MD901 DLBCL and Ramos human BL xenograft mouse models and in a primary **λ-MYC transgenic** mouse BL model [59,64], providing a proof of concept for the therapeutic potential of miR-28 replacement therapy.

The best-studied tumor suppressor miRNA in B cell neoplasia is miR-34a, an miRNA component of the *P53* tumor suppressor network that regulates the cell cycle, apoptosis, and DNA damage

Figure 2. miRNA Delivery Systems. The cartoon shows miRNA delivery systems and tumor-specific targeting systems used to modify miRNA expression in B cell neoplasias. Synthetic nanoparticles: Lipid nanoparticles have a hydrophobic core and a surface modified with cationic polymers that bind small RNA molecules. Polymeric nanoparticles are formed of cationic polymers that condense nucleic acids through electrostatic interactions. Inorganic nanoparticles have a metallic core (e.g., gold), and small RNA molecules are loaded onto the surface through thiol interactions. The surface of all of these synthetic nanoparticles can be modified with polymers such as polyethylene glycol (PEG) and the desired ligand to target tumor cells. EnGenelC delivery vehicle nanocells (EDVs), also called TargomiRs, are bacterial minicells modified with surface-conjugated antibodies to enable specific targeting. Polymer-based systems: Dendrimers comprise positively charged complexes that conjugate nucleic acids with poly(amidoamine) or poly(propylenimine). Polyethylenimine (PEI) is a polymer that forms a complex with nucleic acids and retains a positive charge that allows them to adhere to cell membranes. Viral vectors are usually adenoviral vectors that encode small RNA molecules. Chemical conjugates are formed of naked RNA molecules linked to chemical structures, such as pHLIP (low-pH-induced transmembrane structure), or ligands to increase delivery efficacy and allow cellular uptake [9]. Abbreviation: LPS, lipopolysaccharide.

responses [65–70]. Epigenetic inactivation of the miR-34a promoter through hypermethylation has been observed in **NHL** cell lines and human diagnostic samples, underlying the loss of miR-34a expression in various human B cell neoplasms [71]. In addition, low miR-34a expression is associated with poor prognosis in CLL, DLBCL, mantle cell lymphoma (MCL), and mucosa-associated lymphoid tissue (MALT) lymphoma [72]. Unexpectedly, miR-34a deletion does not accelerate *Myc*-induced lymphomas or increase susceptibility to spontaneous or irradiation-induced tumorigenesis [73], probably reflecting the existence of tumor suppressor pathways able to compensate for miR-34a loss, although this remains to be tested. The therapeutic potential of miR-34a restoration was assessed in ABC-DLBCL and MM human cell lines in mouse xenografts, where tumor growth was strongly inhibited after intratumor or systemic administration of synthetic miR-34a mimics, relative to scramble mimic controls [66,70]. In addition, miR-34a mimics reduced tumor infiltration and increased apoptosis of primary human MM lymphoma cells in severe combined immunodeficient (SCID) mice implanted with **synthetic 3D polymeric scaffolds** previously reconstituted with human bone marrow stromal cells (BMSCs) [70]. These findings suggested that miR-34a mimics could complement human BMSCs in providing a certain protective role against MM *in vivo* in mice.

Collectively, these studies confirmed a causative role for dysregulated miRNA expression in B cell oncogenic transformation and neoplasm maintenance, identifying putative relevant targets for miRNA-based therapies.

miRNAs as Prognostic and Predictive Candidate Biomarkers in B-NHL

Dysregulated miRNA expression is a common event in diverse cancers, including B-NHL. Expression studies should, however, be taken with caution in cases where miRNA expression from GC-derived B-NHL is compared with that of naïve B cells, rather than with that of its nontransformed GC counterpart. This cancer footprint places miRNAs as useful potential molecular biomarkers, and several studies have already explored the promise of miRNA profiling as a prognostic and predictive tool [74]. Some illustrative examples in B-NHL (reviewed in [75–78]) are outlined in Table 2. Some of these studies involve the use of a single miRNA, while others propose using combined miRNA signatures as possible biomarkers to identify clinical outcomes. Expression of a given biomarker in B-NHL might ideally predict survival, relapse, remission, and even responsiveness to a specific treatment once cancer has been diagnosed (Table 2). Accordingly, several biomarkers of lymphoma progression can be detected in blood or serum (Table 2), which could make sample acquisition easier and less invasive than obtaining tumor biopsies. The emergence of miRNAs as valuable candidate biomarkers is reflected in the number of registered clinical trials. For example, miR-34a and miR-194 are being tested in a clinical trial as biomarkers of disease in cell samples from acute myeloid leukemia (AML) patients (NCT01057199[ii]). Moreover, there are clinical studies that monitor miRNAs as predictive biomarkers of clinical response. For example, the expression of miR-150, among other miRNAs, is being tested as a predictive biomarker and assessed at different time points in serum of patients diagnosed with skin diseases such as cutaneous T cell lymphoma (CTCL) and treated with photo (chemo)therapy (NCT03340155[iii]). Similarly, clinical trial NCT01606605[iv], a retrospective and observational study of 350 DLBCL patients, established correlations between miRNA expression and clinical outcome, relapse, and disease progression. miRNA profiling has thus become a clinically fruitful area of investigation to identify potential prognostic and predictive biomarkers for B-NHL.

miRNA-Based Therapeutics

The oncogenic and tumor suppressor functions ascribed to several miRNAs provide a strong rationale for the development of RNA-based therapies aimed at altering miRNA expression in tumors. The first FDA-approved siRNA, Patisiran, was licensed in 2018 for the treatment of a

Table 2. miRNAs as Putative Prognostic and Predictive Biomarkers of Human B-NHL[a]

B-NHL	miRNA	Biomarker utility	Source material	Cohort (*n*)	Refs
CLL	miR-21	Prognostic of OS	Blood	80	[131]
		Predictor of response to fludarabine treatment	Blood	12	[132]
	miR-34a	Predictor of response to fludarabine treatment	Blood	60	[133]
	miR-148a	Predictor of response to fludarabine treatment	Blood	12	[132]
	miR-150	Prognostic of OS/TFS	Blood Serum	273 252	[134]
	miR-155	Prognostic of OS in FCR-treated patients Predictor of response to lenalidomide and FCR treatment	Blood	228	[135]
	miR-181b	Prognostic of OS and TFS	Blood	104	[131]
		Prediction of time from diagnosis to initial therapy	Blood	114	[136]
	miR-222	Predictor of response to fludarabine treatment	Blood	12	[132]
	miRNA signature (miR-23a, miR-23b, miR-24-2 miR-29c, miR-146, miR-155, miR-181a, miR-221, miR-222)	Predictor of the time from diagnosis to initial therapy	Blood	94	[137]
DLBCL	miR-18a	Prognostic of OS in R-CHOP-treated patients	Tissue	176	[138]
	miR-21	Prognostic of OS	Serum	112	[139]
		Prognostic of RFS	Tissue, serum	62	[126]
	miR-22	Prognostic of PFS	Serum	36	[140]
	miR-23a	Prognostic of EFS	Tissue	80	[141]
	miR-27b	Prognostic of OS	Tissue	202	[56]
	miR-125b	Prognostic of OS Predictor of response to R-CHOP treatment	Tissue, serum	56	[142]
	miR-130a	Predictor of response to R-CHOP treatment	Tissue, serum	56	[142]
	miR-146a	Prognostic of PFS	Tissue	121	[143]
	miR-155	Prognostic of PFS Predictor of treatment protocol (CHOP vs R-CHOP)	Tissue	121	[143]
		Prognostic of EFS Predictor of R-CHOP treatment failure	Tissue	79	[62]
	miR-181a	Prognostic of PFS in R-CHOP-treated patients	Tissue	176	[138]
	miR-199a	Prognostic of EFS	Tissue	80	[141]
		Prognostic of OS	Tissue	58	[90]
	miR-222	Prognostic of PFS in R-CHOP-treated patients	Tissue	176	[138]
	miR-497	Prognostic of OS	Tissue	58	[90]
	miR-24, miR-27a, miR-30e-3p, miR-100, miR-199b, miR-302, miR-330 miR-425, miR-608, miR-637	Prognostic of EFS	Tissue	80	[141]
	miR-142, miR-199b, miR-302b	Prognostic of EFS in R-CHOP-treated patients	Tissue	80	[141]
	miR-370-3p, miR-381-3p, miR-409-3p	Predictor of relapse	Tissue	13	[11]
	miRNA signature (miR-224, miR-1236, miR-520d-3p, miR-455-3p, miR-33a)	Predictor of remission Prognostic of OS and PFS	Serum	173	[144]
MCL	miR-18b-5p	Prognostic of OS and PFS	Tissue	172	[145]
	miR-20b	Prognostic of OS	Tissue	54	[146]
	miR-29	Prognostic of OS	Tissue	30	[147]
	miR-223	Prognostic of OS	Blood	11	[148]
	miRNA signature (miR-129-3p, miR-135a, miR-146a, miR-424, miR-450-5p, miR-222)	Prognostic of OS and EFS	Tissue	30	[149]

[a]Abbreviations: EFS, event-free survival; FCR, fludarabine, cyclophosphamide, and rituximab; PFS, progression-free survival; OS, overall survival; RFS, relapse-free survival; TFS, treatment-free survival.

rare polyneuropathy caused by transthyretin-mediated amyloidosis [79]. Although miRNA-based drugs have not yet been authorized in the clinic, several biotech companies are developing miRNA-based candidate drugs, some of which are currently being tested in Phase I and Phase II clinical trials. Below, we comment on the miRNA therapy clinical trials conducted so far in cancer patients (Table 3).

MRX34

MRX34 is a liposome-encapsulated double-stranded RNA (dsRNA) that mimics the human tumor suppressor miR-34 and was the first miRNA-based cancer therapy to enter human clinical trials. The clinical trial NCT01829971[v] evaluated the safety of MRX34 in 85 patients with advanced solid tumors refractory to standard treatment. Although MRX34 treatment showed antitumor activity in 29% of patients in Phase Ia, the FDA halted the Phase Ib study after severe adverse events (SAEs) were reported in five patients who experienced immune-related toxicity, including cytokine release syndrome [80]. The cause of SAEs in these patients remains unclear, but it has been suggested that lipid-based nanoparticles (LNPs) and dsRNAs could cause adverse immune responses [81]. However, the same LNP encapsulation has been used for two other anticancer drugs (PNT2258 and MTL-CEBPA) without provoking immune-related SAEs in Phase I or Phase II clinical trials. PNT2258 is a single-stranded DNA targeting *BCL2* that showed promising results in a Phase I trial in patients diagnosed with advanced solid tumors (NCT01191775[vi]) [82], while MTL-CEBPA is a dsRNA-targeting *CEBPA* [83] that is being tested in patients with advanced liver cancer enrolled in a Phase I trial (NCT02716012[vii]) (according to the 2019 European Society for Medical Oncology Congress). Evidence thus suggests that the use of LNP-mediated delivery or of dsRNA is unlikely to be the cause of immune SAEs observed in the MRX34 trial, but further studies are needed to robustly clarify this issue.

MesomiR-1

A Phase I clinical trial (NCT02369198[viii]) was the first to evaluate a TargomiR drug – an miRNA mimic delivered by targeted bacterial minicells. MesomiR-1 contains a miRNA mimic of the tumor suppressor miR-16 in minicells coated with an epidermal growth factor receptor (EGFR)-antibody to target tumor cells [84]. In this trial, the maximum tolerated dose of mesomiR-1 was assessed in 26 patients with malignant pleural mesothelioma or non-small cell lung cancer (NSCLC) refractory to standard therapy. MesomiR-1 showed an acceptable safety profile and

Table 3. miRNA-Based Therapies in Clinical Trials[a]

Drug/therapy agent	Delivery system	ClinicalTrials.gov identifier	Study design	Phase/trial status	Disease	Refs
MRX34 (miR-34 mimic)	LNPs (smarticles)	NCT01829971[v]	Multicenter, interventional, single group assignment, open label	Phase I (terminated)	Primary liver cancer, SCLC, lymphoma, melanoma, MM, renal cell carcinoma, NSCLC	[80]
MesomiR-1 (miR-16 mimic)	EnGeneIC delivery vehicle	NCT02369198[viii]	Interventional, single group assignment, open label	Phase I (completed)	Malignant pleural mesothelioma, NSCLC	[84,85]
Cobomarsen (MRG-106) (anti-miR-155)	LNA-modified antisense inhibitor	NCT02580552[ix]	Interventional, parallel assignment, non-randomized, open label	Phase I (active, not recruiting)	CTCL (mycosis fungoides), CLL, ABC-DLBCL, ATLL	[86]
		NCT03837457[x]	Multicenter, interventional, single group assignment, open label	Phase II (enrolling by invitation)	CTCL (mycosis fungoides)	
		NCT03713320[xi]	Multicenter, interventional, parallel assignment, randomized, open label	Phase II (recruiting)	CTCL (mycosis fungoides)	

[a]Abbreviations: ATLL, adult T cell leukemia/lymphoma; SLCL, small cell lung cancer.

early signs of antitumor activity in 73% of patients. The results of this trial thus support the development of additional studies based on the antitumor activity of miR-16 in combination with chemotherapy or **immune-checkpoint inhibitors** [85].

Cobomarsen

A Phase I clinical trial (NCT02580552[ix]) studied the efficacy and safety of cobomarsen in patients diagnosed with a subset of hematological cancers. Cobomarsen is a locked nucleic acid (LNA)-based oligonucleotide inhibitor of miR-155. A Phase I clinical trial showed sustained reduction in lesion burden and an acceptable safety profile [86], prompting the initiation of Phase II clinical trials (NCT03837457[x]/NCT03713320[xi]) in CTCL patients to compare the efficacy of cobomarsen versus vorinostat, an FDA-approved drug for CTCL.

Although miRNA-based therapy has to date achieved only partial responses or disease stabilization, it should be noted that the patients enrolled in these clinical trials were predominantly diagnosed with late-stage, relapsed, or refractory cancers. Thus, these results are promising for these patient subsets and support the continuation of miRNA-based clinical trials. In addition, the efficacy of miRNA-based therapy may be improved upon the molecular characterization of patients with a higher probability of exhibiting a clinical response.

miRNA Modulation Can Enhance Sensitivity to Other B Cell Neoplasia Treatments

There is growing interest in the identification of miRNAs that sensitize neoplastic B cells to other antitumor drugs, for use in miRNA-based combination therapy. Several miRNAs increase the sensitivity of human B-NHL to **R-CHOP** chemotherapy components *in vitro* [11,41,87–92]. Lentivirus transduction of miR-370-3p, miR-381-3p, miR-409-3p [11], and miR-34a-5p [89] in human DLBCL cell lines showed decreased cell viability when combined with doxorubicin [11,89] or rituximab [11] compared with scramble-transduced controls. In addition, transfection of miRNA mimics (miR-197 [88], miR-199a-3p, miR-497-5p [90], miR-187 [91]) in human DLBCL cell lines sensitized the cells to doxorubicin [88,90,91] or vincristine [90,91], as measured by decreased cell viability and/or increased apoptosis. In addition, transfection of miR-21 [41,87] and miR-155 [92] inhibitors in human DLBCL or BL cell lines sensitized cells to CHOP [87], doxorubicin [41], or rituximab [92] compared with scramble controls. Increased cell death was triggered by modulation of drug resistance through downregulation of the expression of *MDR1* [41] or *LMP1* [92] or by affecting PI3K/AKT survival pathways [87]. Moreover, human DLBCL xenografts in mouse models showed that overexpression of miR-148b sensitized tumors to CHOP, presumably via an Ezrin rescue-associated mechanism [93]. Together, these studies suggest the potential of miRNAs as chemosensitizers to enhance cancer therapy efficacy.

The increasing understanding of the molecular pathogenesis of B cell lymphoma has led to the development of B-NHL-specific therapies. For example, new algorithms based on gene expression profiles might be used to predict lymphoma subtypes, in turn helping to predict the response to therapy [94]. A number of studies have explored the potential of combining some of these B-NHL-targeted drugs with miRNA modulation strategies. For example, MM cell lines *in vitro* and MM xenografts in mice have shown that overexpression of miR-497 [95] or miR-137 [96] or treatment with miR-145-3p mimics [97] can potentiate the antitumor activity of bortezomib, a proteasome inhibitor commonly used to treat MM, by modulating the expression of apoptotic proteins [95], regulating **DNA damage pathways** [96], or inducing cell death through *HDAC4* inhibition [97]. Furthermore, inhibition of miR-21 in the Sup-b15 ALL human cell line sensitized it to imatinib, a target drug that inhibits tyrosine kinases, inducing apoptosis through upregulation of *PTEN* [98]. Collectively, these studies open a path to achieving improved B-NHL therapy by

showing that, in certain instances, drug sensitivity might be increased when targeted therapies are combined with miRNA modulation approaches.

Immunotherapy has become the gold-standard therapy for several cancers, including B-NHL. Checkpoint inhibitor therapy is usually based on the blockade of negative checkpoints put in place by the interaction of molecules such as programmed cell death-1 (PD-1) with its ligands PD-L1 and PD-L2. Several miRNAs have been shown to regulate the expression of inhibitory cell-surface molecules. For example, transfection with miR-28 mimics attenuated the expression of *Pdcd1* in lymphocytes collected from lymph nodes of B16F10 melanoma-bearing mice [99] and overexpression of miR-195 [100], miR-214 [101], and miR-34a [102] downregulated the expression of *PDCD1L1* (PD-L1) in human DLBCL cell lines. These findings support the potential of using synthetic miRNA mimics or anti-miRs to sensitize tumors to PDL-1–PD-1 blockade. Moreover, the data suggest that miRNA-based therapies might potentially yield improved responses in immunocompetent models compared with those reported using immunodeficient mice, which are the most commonly used mice for B-NHL xenograft models. However, these models remain to be further tested.

Concluding Remarks

Synthetic miRNA mimics or anti-miR molecules are small and of low molecular weight, facilitating their formulation into various types of nanocarriers and conjugates for effective delivery when administrated locally or systemically (Figure 2) (reviewed in [9]). The field will be significantly advanced when accessible, clinically scalable, tumor-specific targeted delivery systems become available to improve the specificity and reduce the toxicity derived from miRNA delivery to non-tumor cells (see Outstanding Questions). Various types of ligands, including functional peptides, antibodies, and aptamers, have already been assessed for their ability to target miRNA and anti-miR carriers to tumors [9]. There are now several miRNA carrier systems useful for cancer therapies: encapsulation of miRNA mimics in bacterially derived minicells targeting cancer cell receptors via bispecific antibodies [85,103], peptide-based miRNA nanoparticles [104]; **micelles** [105]; engineered exosomes carrying ligands for receptors overexpressed on cancer cells [106]; conjugation of miRNA to an oligonucleotide recognized by a myeloid- or B cell-specific receptor [107]; and attachment of anti-miRs to a peptide with a pHLIP that targets the tumor microenvironment [52].

Another important challenge in the field is the assessment of miRNA therapies in preclinical trials using *in vivo* models that more faithfully model human B-NHL. A prominent example is the recently developed **patient-derived xenograft (PDX)** system, which recapitulates the transcriptional, proteomic, and functional processes of both treatment-naïve and relapsed or refractory B-NHL, thus allowing Phase II-like trials in mice [108–110]. These are likely to be the models of choice for the selection and screening of novel miRNA-based treatments based on combinations with currently available B-NHL therapies. In addition, molecular characterization of treated tumors by whole-exome sequencing may allow the identification of dose combinations and administration regimens (combined or sequential) to reduce drug resistance and improve the efficacy of B-NHL therapies. The ultimate goal is to take advantage of the differential mechanisms of action of conventional drugs and miRNA-based therapies. Personalized combination therapies can directly tackle the Achilles' heel of cancer drug resistance, ideally leading to effective treatments for B-NHL patients.

Outstanding Questions

Ongoing research aims to develop technologically accessible and clinically scalable tumor-specific miRNA-based drug delivery systems. Can these systems help to improve the efficacy of miRNA-based therapies and reduce toxicity-associated effects in non-tumor cells?

Patient-derived xenograft (PDX) models can recapitulate many features of the original tumors from patients and more closely reflect human pathology compared with tumor cell-line xenograft models. Might PDX become the gold standard for analysis of the therapeutic efficacy of miRNA-based therapies in preclinical trials *in vivo*?

Can molecular characterization of tumor evolution by whole-exome sequencing facilitate the identification of better miRNA-based drug combinations that reduce tumor growth and drug-resistance selection?

Are we moving towards personalized medicine through the identification of the optimal miRNA-based combined therapy tailored to each B-NHL patient?

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Resources

[i] https://gco.iarc.fr/

[ii] https://clinicaltrials.gov/ct2/show/NCT01057199

[iii] https://clinicaltrials.gov/ct2/show/NCT03340155

[iv] https://clinicaltrials.gov/ct2/show/NCT01606605

[v] https://clinicaltrials.gov/ct2/show/NCT01829971

[vi] https://clinicaltrials.gov/ct2/show/NCT01191775

[vii] https://clinicaltrials.gov/ct2/show/NCT02716012

[viii] https://clinicaltrials.gov/ct2/show/NCT02369198

[ix] https://clinicaltrials.gov/ct2/show/NCT02580552

[x] https://clinicaltrials.gov/ct2/show/NCT03837457

[xi] https://clinicaltrials.gov/ct2/show/NCT03713320

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