In this issue: Non-coding RNAs as potential laboratory biomarkers

The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC

How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market

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ARTICLE INFO

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Key words:
microRNA, diagnosis, therapeutics, cancer, drug development

ABSTRACT

The discovery of miRNAs in the mid-90s has changed the dogma of gene expression regulation. Currently, miRNAs are the main theme of thousands of publications each year and their involvement in human diseases is everyday more deeply understood. With that being known, what are the actual clinical applications of miRNAs and how far are they truly from the patients? To address this question, we reviewed the miRNA diagnostic and therapeutic market. With many companies developing miRNA panels, the activity is high in the diagnostic area. Some products, notably for thyroid cancer (Interpace Diagnostic), are already available to clinician and covered by major insurance companies. In comparison, the therapeutic market, mainly driven by miRNA mimics and antagomiR products, is less advanced. Miravirsen (produced by Roche/Santaris) and RG-101 (produced by Regulus Therapeutics), designed to treat hepatitis C, are considered the flagship products of this class of future

drugs. All of the miRNA-based drugs are currently in clinical trials and none have yet reached the pharmaceutical breakthrough. However, acquisition of miRNA-based companies by major pharmas is sending a positive feedback on their potentials. With multiple initiatives on their way, the next years will definitely be determinant for the miRNA market that is still in his infancy.

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INTRODUCTION

For the last thirty years, the fundamental research into RNA biology has grown at an exponential rate. We are now better positioned than ever to understand the involvement of RNA in almost all critical cellular processes. Indeed, for many years, the number of non-coding RNA discovered has steadily increased. Hence, it is not surprising that several Nobel prizes were awarded for corner stone RNA discoveries, such as those won by Cech and Altman in 1989 (RNA catalytic activities; (1)), Ramakrishnan, Steitz and Yonath in 2009 (ribosome structure; (2)), and of most interest for this review, to Fire and Mello in 2006 (RNA interference; (3)).

Considering the increase in RNA-focused research, one can expect that the advancement of general and specific knowledge about RNA could result in direct clinical applications. For example, more than 45,000 studies were published in 2017 on RNA (Figure 1A). From these, a large proportion of the studies either considered that their work could contribute to the diagnosis or the treatment of disease (about 13,000 and 10,000, respectively; Figure 1B).

From the multitude of RNA discoveries, one of the most important was the discovery of RNA interference by Fire and Mello and miRNAs by Ambros and colleagues (4, 5). Thousands of these small RNAs of approximately 20 nucleotides in length have been identified in humans so far and are conserved across all species (6). Detectable in biopsies and body fluids, miRNAs are considered as very sensitive and specific circulating biomarker (7). The enthusiasm for miRNA in the diagnostics field is reflected by the number of related publications, reaching around 11,000 papers in 2018 (Figure 2A).

On the therapeutic side, polypharmacology is gaining a lot of interest in the pharmaceutical era (8). It is now clear that human diseases are complex and that deregulation of multiple genes is often needed to transform a normal cell into a pathological one (9). Furthermore, redundant cellular pathways can limit efficiency of monogenic targeting compounds (10). Conversely, the miRNA's function is by definition based on multitargeting (11). In fact, it is well established that these small RNAs recognize their mRNA targets mainly by the 2nd to the 8th nucleotides of their 5' end. Mismatches in the 3' sequence allow one miRNA to specifically bind to hundreds of different mRNAs simultaneously regulating their expression (11, 12). It is not surprising that these endogenous multitargeting molecules gained a lot of interest in the therapeutic field. In fact, nearly 3,500 studies were published in 2018 on miRNA-based therapeutics (Figure 2B).

Similarly, a multitude of clinical trials were conducted or are currently underway to test new miRNA based treatments. This effervescence is therefore expressing the evolution of this still young and relatively immature field of utilizing the miRNA as a therapeutic tool.

With thousands of academic publications each year, how far from patients are miRNAs? To answer this question and bring a different angle, we reviewed the market of the diagnostic and therapeutic applications of miRNAs. With a lot of companies offering miRNA-profiling services, our focus was to highlight the ones providing specific expression panels for a given clinical application. On the therapeutic side, multiple clinical trials

Figure 1 Number of studies published in PubMed per year for: (A) RNA studies; (B) RNA diagnostic and therapeutic studies

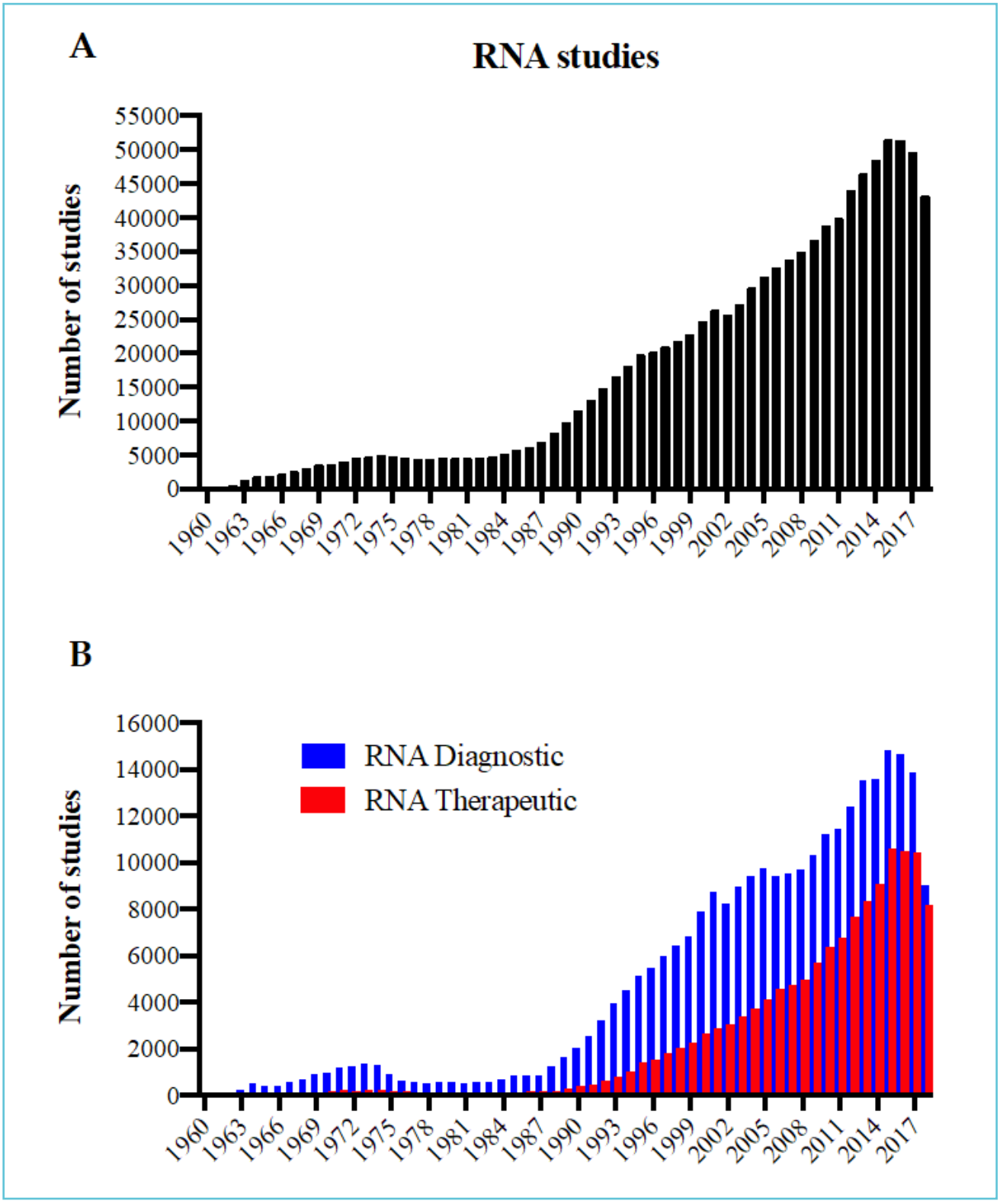
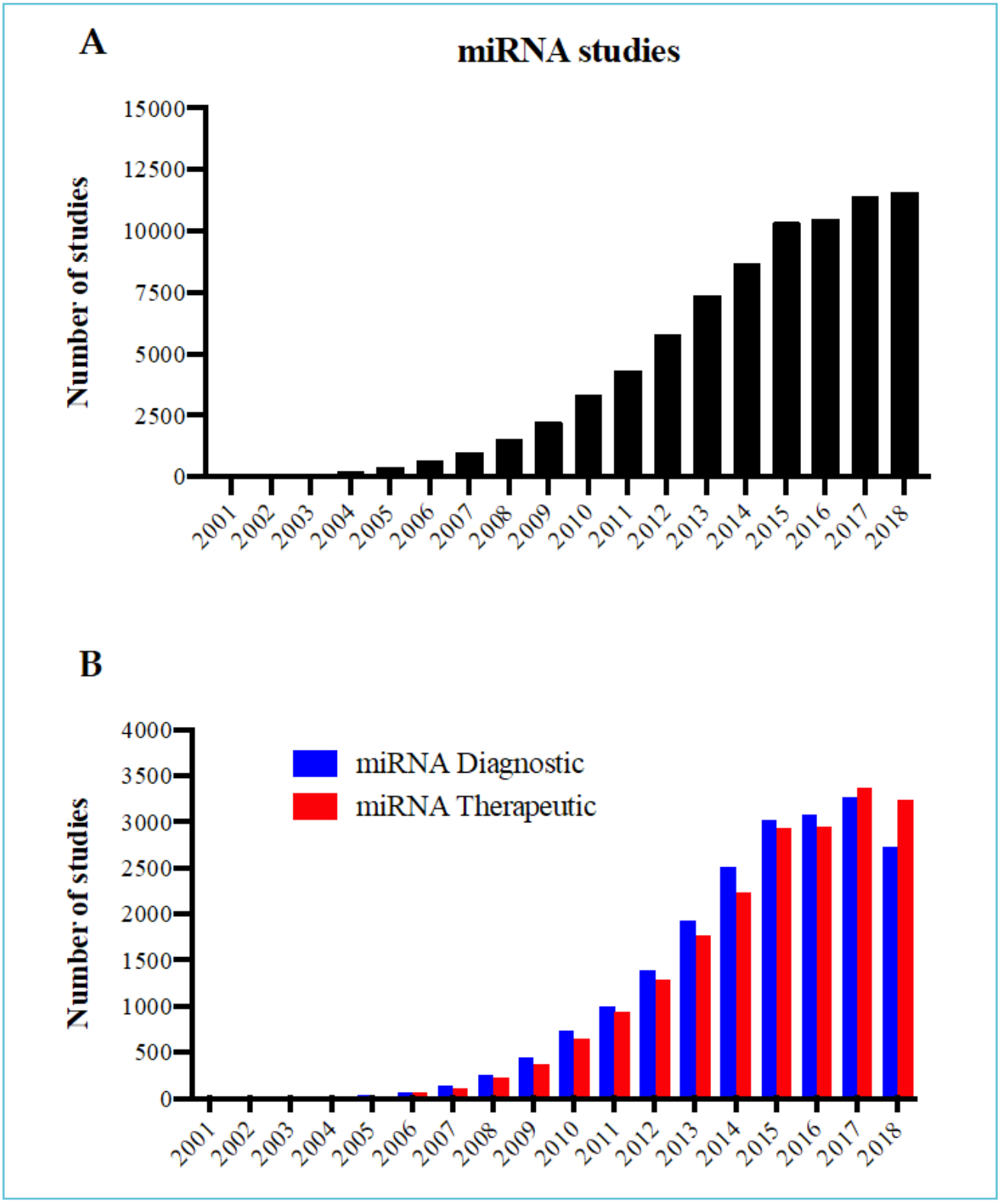


Figure 2 Number of studies published in PubMed per year for: (A) miRNA studies and (B) miRNA diagnostic and therapeutic studies



are currently ongoing and we focused on the products that are the most advanced in the field.

miRNA-BASED DIAGNOSTICS

Applications in the cancer field

Since their initial discovery in 1993, miRNA have showed a great diagnostic potential by being associated with various diseases (5, 7). Since then, the number of publications on the diagnostic potential of miRNA grew almost exponentially (Figure 2B), which attracted numerous companies to develop new miRNA-based diagnostic tools. To our knowledge, the first company focusing on miRNA-based diagnosis assays was Rosetta Genomics (NASDAQ: ROSG), an Israeli company incorporated in early 2000. In partnership with Precision Therapeutics, a personalized cancer therapy company, they launched in 2012 miRview™ mets a miRNA panel allowing the identification of cancers of unknown or uncertain primary origin (CUP) (Table 1).

These cancers account for up to 15% of newly diagnosed cancer in the U.S. every year (13, 14). This CUP classifier was able to identify 42 different tumor types using microarray that measures the expression levels of 64 miRNAs. The miRview™ mets panel was able to identify accurately 90% of the 509 validation sample set. The assay also showed 88% correspondence with the patient's clinicopathological evaluation (14). Based on this success, Rosetta Genomic introduced a new product called RossettaGX Reveal™ (Reveal) in 2016.

This new miRNA classifier relied on qRT-PCR to differentiate between benign or indeterminate thyroid nodules using FNA cytology smears. Reveal's performance was validated using a multicenter retrospective cohort of 189 FNA smears and achieved a negative predictive value of 91%, a sensitivity of 85% and a specificity of 72% (15). Unfortunately, the company declared bankruptcy in May 2018 after a $10 million acquisition deal by Genoptix failed. Interestingly, Interpace Diagnostics acquired most of the equipment through a bankruptcy auction and hired some of Rosetta Genomics employers.

Interpace Diagnostics (NASDAQ: IDXG), is based in New Jersey and is a molecular diagnostic testing company that is offering personalized medicine strategies for the diagnosis of thyroid and pancreatic cancer. Interpace acquired a solution developed by Asuragen combining ThyraMIR®, a miRNA classifier, and ThyGeNEXT®, an oncogene panel for thyroid cancer stratification (Table 1). Initial validation was completed by Asuragen in 2015, over 12 endocrinology centers across the U.S. and 638 surgical and fine needles aspirations (FNA) biopsies were analyzed (16). The combination of ThyraMIR® and ThyGeNEXT® offers an interesting alternative as 15-30% of standard cytological evaluations fail to discriminate benign from the malignant lesions (17, 18). The ThyraMIR® classifier includes the quantification of 10 miRNAs: miR-29b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p, miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375 and miR-551b-3p (Table 1).

This panel was trained using 240 well-characterized, surgically resected, benign or malignant thyroid lesions. A validation set of 54 independent resected thyroid tissues and 235 preoperative thyroid FNAs was then used for threshold optimization (16). Based on this study, Interpace Diagnostic claims a Negative Predictive Value of 94%, a Positive Predictive value of 74% and a reduction of 85% of unnecessary surgeries. Interpace Diagnostic is CLIA certified and CAP accredited, but both tests are not FDA approved. Availability of ThyraMIR® through Labcorp, was announced on January 12, 2016. Interpace also received Medicare coverage in 2016 covering over 50 million patients across the United States. Most recently, in November 2018, the Blue Cross Blue Shield and the U.S. Federal Employee Health Benefit Program have agreed to include

Table 1 Currently active companies working on miRNA-based diagnostics

Companies	Product	Targeted miR	Disease type	Development phase	Reference
Interpace Diagnostics/ Asuragen	ThyraMIR/ ThyGENX	miR-29b-1-5p, miR-31-5p, miR-138-1-3p, miR-139-5p miR-146b-5p, miR-155, miR-204-5p, miR-222-3p, miR-375 and miR-551b-3p	Thyroid and pancreatic cancer	Available	thygenext-thyramir.com
Rosetta Genomics/ Precision Therapeutics	miRview mets	miRNA library	Identify tumor origin of cancer	Available	rosettagenomic.com oncotest.co.il
Genoptix	Reveal	miRNA library	Thyroid	Available	genoptix.com
TAmiRNA	OsteomiR	Panel of 19 miRNAs	Osteoporosis	Available	tamirna.com
TAmiRNA	ThrombomiR	Panel of 11 miRNAs	Cardiovasc. Disease	Available	-
Hummingbird Diagnostics	-	Panels (unknown)	Multiple (cancers, brain, heart)	Pre-Clinical & Phase 1	hummingbird-diagnostics.com
DiamiR	CogniMIR	Panel (unknown)	Alzheimer	Phase 1	diamirbio.com
	Others	Panel (unknown)	Brain diseases		
Mirnext		Panel with miR 423-5p	Heart failure	Development	hmirnext.com
Quanterix/ DestiNA Genomics	Simoa	miR-122	Liver toxicity	Pre-Clinical	quanterix.com

the ThyGeNEXT®/ThyraMIR® combined tests for their 5.3 million beneficiaries.

Hummingbird Diagnostics (formerly known as Comprehensive Biomarker Center) was founded in 1998 in Heindelberg, Germany, and has now extended to Boston, Massachusetts, in the United States. Operating as a subsidiary of Febit Holding, this company is hands-on in the development of novel miRNA signatures in liquid biopsies for early detection of various diseases, ranging from cancer (Non-small-cell lung carcinoma, melanoma, breast cancer), to neurodegenerative (multiple sclerosis, Alzheimer, Parkinson), cardiovascular (acute myocardial infarction and heart failure) and inflammatory bowel disease (19-21). With its DIN EN ISO/IEC 17025:2005 accreditations for RNA (including miRNA) extraction and microarray services (Agilent Certified Service Provider), the company profiled more than 7,000 disease-related body fluid samples so far. The bioinformatics and statistical processing of those large expression data led to the identification of multiple disease-related miRNA panels (Table 1). Although none of these are currently commercially available, Hummingbird Diagnostics has 17 granted patents in the field of whole blood expression profiling. The clinical validation of their miRNA signatures for early diagnostic use are ongoing with the funding received through their participation in three European FP7-funded consortia (BestAgeing, RiskyCAD and EURenOmics).

Applications in age-related diseases

DiamiR is located in Monmouth Junction, New Jersey and published their first article describing the use of miRNA biomarkers in mild cognitive impairment in 2012 (22). DiamiR have since published several articles with a similar scope, which is the use of miRNA as markers of neurodegenerative and neurodevelopmental disorders (23-25). This work was funded in part by the Michael J. Fox Foundation for Parkinson's Research and through a Small Business Innovation Research (SBIR) phase II grant of $1.5M from the National Institute on Aging (NIA) of the National Institutes of Health (NIH) in 2014 and 2015. More recently, in March 2017, the NIA of the NIH awarded DiamiR another SBIR Phase IIB grant of $2.75M over three years to further support the development of their branded lead product, CogniMIR™ (Table 1). CogniMIR™ is currently in clinical trial testing for early detection of Alzheimer's disease at the presymptomatic, mild cognitive impairment and dementia stages. Using different brain-derived miRNA signatures, DiamiR also expects to test for Parkinson's disease, frontotemporal degeneration, and amyotrophic lateral sclerosis. However, those products are still in the validation process.

TAmiRNA is another European leader in miRNA diagnostics that was founded in 2013 as a spinoff of two Austrian companies, BOKU and Evercyte. This R&D company develops and offers validated microRNAs panels as additional tools for the diagnostic of age-related disorders. Funded by AWS Seedfinancing and EU Horizon2020 programs, TAmiRNA demonstrated the clinical utility of their licensed miRNAs as biomarkers in osteoporosis (26). OsteomiR™ is their lead product intended to provide the risk of a first fracture in female patients with postmenopausal osteoporosis and type-2 diabetes (27-29). The integration of the expression level of 19 blood-circulating miRNAs gives a calculated fracture-risk index that could be used for preventive therapy and treatment follow-up. Similarly, TAmiRNA also proposes the ThrombomiR™ panel (11 miRNAs) to assess platelet function and the ToxomiR™ panel (19 miRNAs) to evaluate the toxicity occurring in various tissues (Table 1). Kits based on primer-coated qPCR plates can be either purchased (except ToxomiR™) or samples can be directly processed by TAmiRNA, from extraction to data analysis. By starting a partnership agreement with SimplicityBio in February 2017,

development of additional miRNA panels are expected. The Swiss-based bioinformatics company has a robust in silico biomarker identification pipeline that could accelerate TAmiRNA's main goal in offering advanced miRNA markers for the diagnosis and prognosis of age-related disorders.

Applications in cardiac function and liver toxicity

Mirnext is a Dutch biomedical company based in Amsterdam that is interested in the diagnostic potential of miRNAs. It was established in 2014 as a new entity of ACS Biomarker, which was built on the Galectin-3 biomarker of heart failure (30, 31), now out-licensed to BG Medicine and available in clinics. Mirnext is currently financed through Life Sciences Fund Amsterdam and Limburg Ventures, two venture capital investors of The Netherlands. Similar to ACS Biomarker, Mirnext's main goal is to identify and commercialize biomarkers in the cardiovascular field but with full dedication towards miRNAs. Their high-throughput, disease-based miRNA profiling identified, among others, miR423-5p as a useful marker of heart failure (32). Together with other clinically relevant miRNAs, Mirnext pursued their validation in large patient cohorts with different cardiovascular diseases including heart failure, coronary artery disease and myocardial infarction. Thus, their miRNA panel integrates many different disease mechanisms useful for the identification and stratification of those pathologies. In addition to the diagnosis of heart diseases, Mirnext is aiming to evaluate cardiovascular risk profiles (mortality, hospitalization) of the individuals tested as part of their multi-marker heart failure test. A single test is expected to provide the clinician extensive information on the patient's cardiovascular health to initiate targeted treatments. At the time of this writing, we were unable to access the company's website.

Quanterix (NASDAQ QTRX) is a biotech company founded in 2007 in Lexington, Massachusett. Through the development of their ultra-sensitive digital biomarker detection technology Simoa®, Quanterix provides healthcare researchers the ability to investigate the continuum of disease progression. In March 2018, they announced a collaborative effort with DestiNA Genomics to enhance RNA biomarker detection. DestiNA was founded in 2010 in Edinburgh, United Kingdom, where they developed and patented a unique PCR-free, chemical-based technology for the detection and quantification of nucleic acids such as miRNAs, without prior isolation from serum or plasma (33, 34). This highly-specific nucleic acid detection combined to the ultra-sensitive Simoa® system provides a solid support for disease-related miRNA biomarker testing. Accordingly, the collaboration's first initiative was focused on miR-122 as a liver toxicity marker (35, 36). They demonstrated that their assay detects miR-122 earlier and outperforms the current protein-based biomarkers in specifically detecting and quantifying liver toxicity.

miRNA-BASED THERAPEUTICS

Several pharmaceutical and biotech companies have launched miRNA projects in their development pipeline (Table 2). Companies are mainly working on two types of products; miRNA mimics and antagomiRs. The miRNA mimics are used to re-establish the concentration of a specific miRNA suppressed by the evolution of a given pathology (37, 38). Inversely, antagomiRs are used to suppress the function of specific miRNAs overexpressed and mechanistically involved in a disease (37, 38). In order to allow the development of miRNA therapeutics, scientists must address two main challenges: the stability and delivery. First, RNA molecules are quite unstable because of their 2'-OH chemical group (39). Therefore, several companies, such as Dharmacon, BioSyn and GenScript, can

Table 2 Currently active companies working on miRNA-based therapeutics

Companies	Product	Targeted miR	Disease type	Development phase	Reference
Roche/Santaris	Miravirsen	miR-122	HCV	Phase 2	roche.com
Regulus Therapeutics	RG-101	miR-122	HCV	Phase 2 (hold)	regulusrx.com
	RG-012	miR-21	Alport syndrome	Phase 1	
	RG-125	miR-103/107	NASH	Phase 1	
MiRagen Therapeutics	MRG-201	miR-29b	Fibrosis	Phase 2	miragentherapeutics.com
	MRG-106	miR-155	Lymphoma and leukemia	Phase 1 and Phase 2	
	MRG-107	miR-155	ALS	Pre-Clinical	
	MRG-110	miR-92	Ischemia	Phase 1	
ENGeneIC	Mesomir	miR-16	Mesothelioma	Phase 2	engeneic.com
Abivax	ABX464	miR-124	IBD	Phase 2	abivax.com
Synlogic	Screening				synlogictx.com
Opko	Screening				opko.com
Alnylam Pharmaceuticals	Screening				alnylam.com
Interna Technologies	Screening				interna-technologies.com
Mello Biotech	Screening				mellobiotech.com

produce natural and chemically modified RNA (2'-O-methyl; 2'-OMe, locked nucleic acid; LNA, of 2'-fluor; 2'-F, phosphorothioate; PS) to stabilize and reduce the high reactivity of RNA molecules. The other major challenge is the delivery of these RNAs to the desired site of action (39). Therapeutic application requires the correct delivery of the RNAs to the targeted organs in order to maintain adequate treatment specificity. When a treatment requires a systemic

delivery through intra-venous injection, the delivery strategies are either passive or active (40, 41). The passive strategy utilizes the tendency of several organs, like the liver, the spleen and the lymph nodes to internalize accumulated particles. Using this non-specific approach, designed nanoparticles or liposome-like particles incorporating RNAs can be targeted to these organs (40, 41). Inversely, the active strategies combine the RNA or the particle with a specific molecule that will bind to the cells of interest and will be endocytosed (40, 41). These structural and delivery challenges, albeit being constantly addressed by new design strategies, still complicate the development of miRNA therapeutics.

Applications in liver disease

Among the most advanced products, there is Miravirsen (or SPC3649), an antagomiR targeting miR-122. Santaris Pharma initially developed this drug candidate before Roche acquired the company in 2014 to expand its RNA therapeutic research and development department (Table 2). Miravirsen is a locked nucleic acid (LNA) containing phosphorothioate modifications. MiR-122, is known to be essential in the life cycle of hepatitis C virus (HCV) expressed in the liver (42, 43). Reducing the activity of miR-122 in the context of HCV infection is important. In fact, miR-122 is a host factor that binds to the 5'-UTR region of the HCV genome and enhances its transcription (43, 44). In phase 1 clinical trials, some patients who received high doses of Miravirsen in monotherapy resulted in undetectable HCV RNA levels (43, 44). Because Miravirsen is a modified RNA (LNA and phosphorothioate), it naturally accumulates in the liver and does not require special delivery strategy. Miravirsen is currently undergoing multiple phase 2 clinical trials.

Another product was developed to target miR-122, RG-101, and is produced by Regulus Therapeutics (NASDAQ: RGLS) in collaboration with Ionis Pharmaceuticals and GSK (Table 2). RG-101 is an N-acetyl-D-galactosamine- conjugated RNA antagomiR that also targets miR-122 in HCV infected hepatocytes (45). RG-101, like Miravirsen, shows considerable efficacy with patients displaying undetectable HCV RNA levels (45). However, some serious adverse events of severe jaundice were recently declared in a clinical trial and the FDA put the studies on hold until the situation is clarified. It is worth mentioning that Regulus was also working on RG-125 (also described as AZD4076), an antagomiR targeting miR-103/107, in phase 1 clinical trial for treatment of nonalcoholic steatohepatitis (NASH; Identifier NCT02612662 and NCT02826525) as well as RGLS5040, an anti-miR-27 aiming to reduce cholestatic diseases. However, development of these latter two were recently suspended.

Applications in fibrotic disease

Regulus has also worked with Genzyme (Sanofi) to test the efficacy of RG-012, an antagomiR against miR-21, which reduces the fibrogenesis of organs associated with Alport syndrome (46). This is an X-linked disease and is characterized by kidney disease, hearing loss and visual impairment caused by mutations of the genes encoding type-IV collagen (47). The use of a modified single-stranded antagomiR with phosphorothioate, 2'-O-methoxyethoxy and constrained ethyl modifications showed an important improvement in the survival of a Alport mouse model with a reduction of kidney disease progression (46). Despite interesting results, the phase 1 clinical trial of RG-012 has recently been discontinued mid-2018 because of the reorganization between Regulus and Sanofi (Clinical trial identifier NCT03373786).

Another promising company is MiRagen Therapeutics (NASDAQ: MGEN), based in Boulder, Colorado. First, the company developed MRG-201, also known as Remlarsen, a miRNA mimic

that aims to restore the levels of miR-29b, which is a negative regulator of the extracellular matrix deposition processes. The miR-29 family (miR-29a/b/c) is constantly downregulated in fibrotic diseases. MRG-201 is an LNA RNA mimic that is administered by intradermal injection and the phase 2 clinical trial is currently underway (Identifier: NCT03601052). Remlarsen could virtually be used for the treatment or prevention of pathological cutaneous fibrosis, as well as of other fibrotic diseases, including idiopathic pulmonary fibrosis (48).

Applications in cancer

While some companies are having great successes, others struggle to positively impact patient outcomes. This was the case of MiRNA Therapeutics (NASDAQ: MIRN) and a miRNA mimic, MRX34. MiR-34, is a well characterized tumor suppressor downregulated in a broad range of cancers (49-51). MRX34 was delivered as a double stranded RNA encapsulated into a liposome-formulated nanoparticle. Preclinical studies were promising when used in several cancer types such as renal cell carcinoma, acral melanoma and hepatocellular carcinoma (52). However, the FDA halted their phase 1 clinical trial when many immune-related serious adverse events leading to death were registered. It reached a point where MiRNA Therapeutics reduced its staff before Synlogic Inc (NASDAQ: SYBX) finally acquired it in 2017.

MiRagen Therapeutics is actively developing MRG-106, also known as Cobomarsen, an LNA antagomiR that targets miR-155. This miRNA is involved in the differentiation and proliferation of blood and lymphoid cells. Cobormarsen is actually involved in phase 1 trials (Identifier NCT02580552) and phase 2 clinical trials (Identifier NCT03713320), with the goal of treating certain types of lymphoma and leukemia (53). Similarly, MRG-107 also targets miR-155 to alleviate symptoms associated with amyotrophic lateral sclerosis (ALS) but has not yet entered clinical trials. In an ever-growing pipeline, they also work on MRG-110 in collaboration with Servier. This LNA antagomiR targets miR-92 in order to treat ischemic conditions such as heart failure (48). Its phase 1 clinical trial is currently recruiting (Identifier NCT03603431).

Pharmaceutical and biotech companies are heavily engaged in developing successful products and RNA biologics are closer than ever to entering the market. Another indicator of this effervescence is the acquisition of RNA-based companies by pharmaceuticals giants. Santaris Pharma was acquired by Roche in 2014, SiRNA Therapeutics by Merck in 2007, followed by the acquisition of this division by Alnylam Pharmaceuticals in 2014, and more recently MiRNA Therapeutics by Synlogic Inc. However, even more companies are currently testing new miRNA therapeutics. For example, ENGeneIC is currently designing and producing Mesomir, a miRNA mimic that aims to replace miR-16, a tumor suppressor that is reduced in cases of cancer, such as malignant pleural mesothelioma (54). It successfully completed phase 1 clinical trial and will soon start phase 2 (55). On another hand, Abivax produces ABX464, a small molecular compound that triggers the increase of miR-124 to reduce the symptoms of inflammatory bowel disease for patients refractory to anti-TNF biologics and corticosteroids. It is currently in preparation for a phase 2b clinical trial for ulcerative colitis and phase 2a for Crohn's disease.

Finally, a multitude of companies work in preclinical and large screening studies to identify potential biologic miRNA such as Opko with their CURNA program, Alnylam Pharmaceuticals, Interna Technologies and Mello Biotech. These companies could therefore increase, in the next several years, the number of miRNA therapeutics being tested or entering the market.

CONCLUSION

Enthusiasm, promise and hope are evident in the miRNA industry. As described, multiple companies are dedicating significant efforts and resources to develop miRNA-based products. The diagnostic field is definitely the most advanced with some miRNA panels already offered to clinicians and covered by major insurance companies. However, considering the thousands of publications in this area, miRNAs as diagnostic products can still be considered in their infancy. On the therapeutic side, despite the potentials, the miRNA-based therapeutic breakthroughs have not arrived yet. Recently, an analytical model based on technological growth metrics showed that miRNAs still require time to reach the maturity point needed to yield a significant number of products that could enter the market (56). For this reason, most of the technologies discussed are currently in clinical trials.

The development and commercialization of new diagnostic and therapeutic tools is definitely a long process. Considering the first evidence of the involvement of miRNA in human disease in 2002 and the first detection of miRNAs in blood in 2008, only a decade later, tremendous progress and effort has been made to bring these small RNAs from the bench to the bedside (57, 58).

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