Nano-trafficking 'Molecular Scissors': Current Trends in miRNA-Based Cancer Metastasis Therapy

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To fight cancer, a novel approach used by researchers is to target the oncogenic gene products with molecular scissors, namely miRNAs. These are small non-coding RNAs that can target the products of harmful genes and promote their degradation. However, the delivery of these small, efficient RNAs is highly problematic. It faces multiple challenges, the major one being effective delivery of the target RNA to its specific site of action without degradation. Once this target RNA is in the in vivo environment, it is susceptible to nucleases and other defense mechanisms, so the first step in ensuring successful cancer therapy with miRNA is ensuring safe and sound delivery to the target cells. This can be achieved using potent and efficacious delivery vehicles that deliver RNA to its target cell and protect it from the challenges of the *in vivo* environment. The stronger the vehicle, the greater the likelihood of success. MicroRNAs (miRNAs) are potential regulators of cancer metastasis since they are able to regulate several genes related to tumour invasion and migration, epithelial–mesenchymal transition and metastatic progression. Recent studies have suggested the use of miRNA replacement and inhibition therapies, especially when delivered to the tumours using nanocarriers with enhanced stability and cellular uptake. However, clinical translation is a challenge: of the 66 evaluable patients in a Phase I trial of the liposomal miR-34a mimic MRX34, 3 had partial responses and the trial had to be stopped due to serious immune-mediated adverse events leading to 4 deaths in 85 enrolled patients. These results highlight the necessity to develop safe delivery systems and enhance tumour targeting. This critical integrated review of the mechanisms of metastasis-associated miRNAs, treatments, nanocarriers, and clinical evidence, coupled with emergent solutions for overcoming delivery and safety barriers, portrays priorities for the translation of miRNA-based treatments to succeed in cancer treatment.

Keywords: cancer therapeutics; delivery agents; miRNA; nanocarriers; nanoparticles.

Introduction:

A modern approach to treating the most debilitating of diseases: Cancer is nano-therapeutics [1]. Combining nanoscale structures with a larger surface area and lesser volume that can easily penetrate and target specific cells and move around, evading the immune system with gene-silencing molecular tools, "the micro RNAs," is a novel approach that has been employed by researchers to treat cancer. Cancer develops when abnormal cells grow uncontrollably and may invade other tissues and then starts creating micro colonies over the entire body, is responsible for a large number of deaths worldwide [2]. A cancer diagnosis can have serious consequences, making effective treatment an important research priority. So, researchers all over the world have been focusing on ways to combat cancer using available therapeutic strategies. The present scenario presents microRNAs as an area of therapeutic interest. MicroRNAs (miRNAs) are small 16-30 nucleotide-long non-coding RNAs that were identified for their regulatory roles in controlling gene expression and repression [3]. They regulate genes by attaching to specific target mRNAs and allowing their cleavage, thus repressing protein production.

They have been identified to modulate and attune processes like cellular development, differentiation, proliferation, survival, and most importantly, cell apoptosis by molecularly turning genes on and off [4]. They encompass a family of RNAs that include small nuclear RNA (snRNA) involved in RNA splicing, small nucleolar RNA (snoRNA) involved in modifications of rRNA, and small interfering RNA (siRNA), which is also responsible for gene regulation, like miRNAs [5]. Their role in controlling gene regulation and mechanisms responsible for cell death and differentiation highlights their importance in cancer onset [6]. Cancer itself is the loss of control over mechanisms that govern the cell cycle; the switches that turn cell division on and off get deregulated, resulting in the genesis of an unregulated mass of cells, leading to cancer in the long run. These switches are actually oncogenes and tumor suppressor genes, so cancer is nothing but a genetic imbalance between oncogenes and tumor suppressor genes [7].

The current review emphasizes the potential role of miRNAs as a panacea for the majority of cancer types by controlling the expression of cancer-related genes[8] . This genetic control can only be exercised if one has the right vehicle for the monitored trafficking of these molecular scissors safely to the target cells. A variety of delivery vectors have been used over the years: lentiviral, retroviral, and liposome-mediated transfection [9]. In fact, efforts have been made for the non-liposome polymer-mediated transfection of target drugs, miRNAs, and siRNAs to the precise location, but all these efforts are cumbersome and require the synthesis of complex molecules [10]. The concept of nanocarriers: particles with size ranges over 1-100 nm in at least one dimension, is receiving increasing attention in the therapeutic field. Nanocarriers include a range of delivery tools, including lipid-based, polymeric and inorganic systems that show much better transportation ability than their counterparts [11]

These nanocarriers can be of metals, metal oxides, or natural polymers that can efficiently transport miRNAs to the target cells for gene silencing [12]. The quest for remedying cancer using nanotechnology is not at all new; efforts to target and kill cancer cells with cancer drugs conjugated with nanoparticles have been done over and over with promising results in some studies compared to when naked drugs were used. However, some transformed cells evade this coup and develop a micro-colony elsewhere, leading to cancer metastasis. Almost 400 Nano therapeutics have been under clinical trials, and we expect to see a rise in the number of Nano medicines in the upcoming years [13]. Nanotherapeutics represents a promising area of medical research with high hopes of treating cancer using

personalized, mutation-specific nano-drugs. However, using siRNA and miRNAs conjugated with nanoparticles can target a related set of oncogenes that malfunction in a certain cancer type, thus improving chances of curing cancer, as it's a heterogeneous set of diseases [14].

The purpose of the review is to present a complete and critical assessment on the therapeutic value of microRNAs (miRNAs) in cancer metastasis, highlighting miRNA molecular mechanisms of action and translational applications. It addresses the regulation of oncogenic and tumour suppressive miRNAs in the invasion, migration and EMT of cancer cells and their role in the metastatic process, as well as the rationale behind miRNA inhibition and replacement strategies for use in the clinic.

Special attention is given to the recent progress made in the development of nanocarriers for the delivery system, with a special focus on the development of nanocarriers that improve the stability and bioavailability of miRNAs, their cellular uptake, tumour-specific targeting, and therapeutic efficacy. In addition, the review critically examines preclinical and clinical studies, highlights the major challenges associated with efficiency of delivery, off-target effects, immunogenicity and safety, and provides an overview of the new technological approaches to address these challenges. This review aims to give a mechanistic and translational link in understanding the biology of miRNAs and designing their delivery systems for improved safety and efficacy of miRNA therapeutics in metastatic cancer treatment.

Novelty Statement:

Not like other reviews which mainly discuss miRNA biology, individual therapeutic miRNAs or nanocarrier platforms separately, this review brings together the mechanisms of metastasis associated miRNAs (masc miRNAs) with therapeutic inhibition and replacement strategies, and the design of platforms for miRNA delivery in cancer therapy. It is unique in that it provides a critical evaluation of the importance of properties of nanocarriers on miRNA stability, cell internalization, tumor targeting, safety and therapeutic activity based on evidence provided in experimental models and human clinical trials. Also, it relates the existing problem of delivery limitations to new strategies for increasing the specificity of delivery and decreasing toxicity. This review brings together the molecular mechanisms of metastatic tumor progression and delivery-platform performance, and clinical feasibility, for the production of safer and more effective miRNA-based therapeutic strategies for metastatic cancer.

Mirans Discovery:

miRNAs are endogenous RNAs that comprise almost 1 % of the human genome [15]. They are known for their highly conserved nature throughout the living world, be that animal, plants, fungi, or even viruses. miRNAs were uncovered for the first time in *Caenorhabditis elegant (C. elegans),* namely lin-4 and let-7, and their importance in cellular development and regulation was noted; since then, over hundreds of miRNAs have been recognized across species, highlighting their conserved nature [16].

The discovery and specific targeting of translation at a particular point provided a hint of its prospective role in gene regulation. Let-7 was discovered in the year 2000 in the same worm, [17]This RNA is responsible for metamorphosis between developmental stages of worms, specifically from stage 4 of development to the adult stage 20-22 [18]. Let-7 acts by physically attaching to the 3' UTR of lin-41 and hbl-1 (lin-57), and prevents this transition. The discovery of another miRNA provided clear enough proof that a new gene regulation phenomenon was apparently hidden for centuries [19]. A search for small RNAs then started across species, with many orthologues and homologues readily detectable in unrelated species too. Almost a quarter of the human proteome is regulated via miRNAs. The discovery of microRNA (miRNA) has gone from traditional cloning to high throughput small RNA

sequencing and computational prediction, allowing known and potentially novel miRNAs to be identified [20].

They are characterized by typical precursor hairpin motifs, sequence conservation, expression patterns and experimental validation [21] Based on their genomic location, biogenesis pathway and biological function, miRNAs can be categorized into several groups, including oncogenic miRNAs (oncomiRs) and tumour-suppressive miRNAs [22]With the development of the sequencing technology and bioinformatics resources, miRNA annotation and functional characterization have been significantly improved, enabling identification of metastasis-associated miRNAs and potential therapeutic targets [23]. However, experimental evidence is needed to determine whether a computational prediction is true of a particular miRNA and to differentiate it from other small RNA molecules.

miRNAs have been classified into some families based on their location on chromosomes and their functions inside cells. Identification of possible miRNA targets helps in determining the fate of miRNAs, which are conserved between the intronic regions of both protein-coding and protein-non-coding genes; they are also found to be clustered either within 3' UTRs of some mRNA genes, or within the exons of non-coding mRNA. Sometimes miRNA genes are found clustered together, as in the case of 54 novel miRNAs grouped on a segment of chromosome 19 [24].

The classification of miRNA into families based on their roles in biological processes or on their sequence homology helps us target a type of miRNA according to the process we want to control. For example, it is known that the miR-34 family can regulate cancer and apoptosis. The miR-200 family is involved in inhibiting metastasis by preventing epithelial-mesenchymal transition (EMT), whereas the let-7 family has been found to control cellular death mechanisms in human cancer cells. These families are identified based on the first 2-8 nucleotides that encompass the 5' position of the miRNA. It is this 5' end that determines the overall stability and correct loading onto the miRISC complex. So identification of miRNA targets (i.e. complementary 3' UTR sequences in mRNA) uses 'miRNA seed' comprising the first 2-8 base pairs of mature miRNA [25].

These algorithmic tools have helped us determine that a single miRNA possesses the ability to recognize and bind to as many as 200 gene target products: the target mRNA. Data from these studies report that a single miRNA can act as a regulatory target to as many as 200 functionally diverse gene targets, thus controlling around a quarter of the human mRNAs [26].

Biogenesis of miRNAs:

Biochemical analysis provides a primary perception regarding the molecular and genetic conception of miRNA biogenesis [27]. The synthesis of miRNA can be categorized broadly into two individual events; firstly, the nascent (ncRNA) or pri-miRNA transcript is synthesized, followed by processing of this ncRNA into a 70- nucleotide precursor. The nascent miRNA comes either from sequences within introns of both protein-coding and non-coding genes and thus is regulated via those gene promoters. Secondly, the pre-miRNA is cut by the molecular scissors to a 21-25 base pair long fully developed miRNA [28]. The pri-miRNA transcript that originates from the transcription of its specific host gene via RNA polymerase II is cleaved by a (ds)-RNA-specific ribonuclease, "Drosha," an RNase III enzyme, using a microprocessor complex, DGCR, that converts this pri-miRNA to 70-nucleotide-long, short, hairpin-loop-shaped precursor miRNA (pre-miRNA)[29].

This initial processing occurs within the nucleus, from where the premature miRNA is transported through an exportin-5-RanGTP-dependent mechanism to the cell's cytoplasm. Within the cytoplasm, another molecular scissor, Dicer, along with the help of TRBP and

AGO2, cleaves the pre-miRNA molecule to a mature miRNA comprising 19–21 nucleotides. miRNA-miRNA duplex is unwound via an unwinding enzyme, helicase, producing a single-stranded mature miRNA [30]. This mature miRNA attaches to a silencing complex known as the miRNA-associated RNA-induced silencing complex (miRISC) [31].

These mature, completely processed miRNAs bind to the 3' UTR of mRNA via complementary regions and thus are involved in gene regulation via cleaving mRNA or translational repression of mRNA. A single miRNA can regulate multiple gene targets, and similarly, multiple miRNAs can regulate and target a single gene [32]. A detailed overview of the entire process of miRNA biogenesis is shown in Figure 1. Biogenesis of microRNA (miRNA) is a coordinated step-wise process in both the nucleus and cytoplasm. Initially, RNA polymerase II transcribes miRNA genes to primary miRNAs (pri-miRNAs), which are subsequently cleaved in the nucleus by the Microprocessor complex [33], which is composed of RNase III endonuclease Drosha and the RNA binding protein DGCR8 that recognizes the hairpin structure and helps in accurate cleavage to produce precursor miRNAs (pre-miRNAs) [34]

Exportin-5 carries these to the cytoplasm with Ran-GTP. Then, another RNase III called Dicer cuts the pre-miRNA into a short RNA duplex [20]. The one strand is loaded into an Argonaute (AGO) protein, which is a central part of the RNA-induced silencing complex (RISC), and the other strand is basically discarded. The mature miRNA directs AGO to the complementary sequences in the mRNA of a complementary target, causing translational repression or mRNA degradation [35]. Dis-regulation of these processing mechanisms may affect the expression of genes and play a role in the development and spread of cancer.

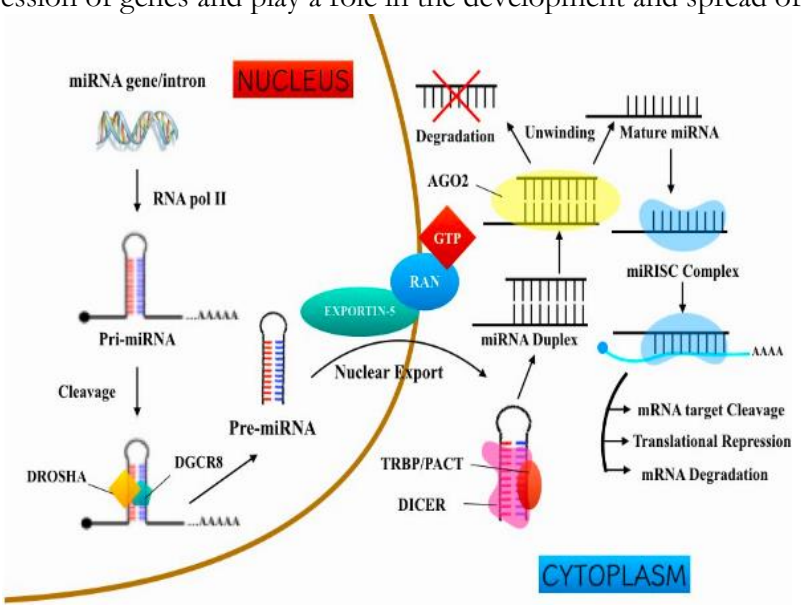

Figure 1. The mechanism of biogenesis of miRNA. This image has been produced using the concept taken from[16]

Functional dysregulation of miRNAs due to mutations or other reasons can contribute to the deregulation of some cellular processes that are controlled by miRNA-mediated mRNA cleavage. This can often lead to tumor onset and cancer progression. As has been previously mentioned, a number of miRNA families are involved in controlling important processes like apoptosis, cellular differentiation, etc. So by controlling miRNA expression, we can control a variety of deregulated cellular processes and potentially influence processes involved in cancer development [36].

Role of miRNA in Controlling Metastasis:

Determining Targets:

miRNA, like siRNA have complex roles; they are involved in both cancer repression and cancer onset, so selecting the miRNA before its targeting is the first important step that should be considered. miRNAs can be categorized broadly as oncogenes and tumor suppressors depending on the type of gene whose expression they control [37]. miRNAs are known to control and regulate cell growth and death (apoptosis). miR-15 and miR-16 induce apoptosis by controlling the expression of an anti-apoptotic gene, B cell lymphoma 2 (BCL2), through targeting its mRNA [38]. This gene plays a pivotal role in a variety of human cancer types, such as leukemia, lymphoma, carcinoma, etc. Another study conducted by showed development of tumorous outgrowth in Drosophila eyes due to misexpression of miR-278 [39]

Not just miRNA but complications in the components of their machinery (proteins, transcription factors, Dicer, Drosha, or export) can also be responsible for tumorigenesis [40]. Downregulation and ultimately reduced expression of DICER resulted in shortened postoperative survival and led to transformation of lungs in non-small cell lung cancer patients (NSCLC) [41]. Expression of DICER is down-regulated in several lung cancers [42]. [43]examined 67 non-small-cell lung cancer samples and checked the RNA expression profile of DICER & DROSHA.

It was observed that a decrease in expression of DICER is directly correlated with a decrease in post-operative survival, which further highlights that DICER might be able to prevent cell transformation [44]. Studies indicate an indirect role of Dicer in cancer by directly regulating miRNA levels. Another RISC protein, Argonaute, that is involved in miRNA and miRNA-based gene regulation has been implicated in its potential role in different cancer types. Three human Argonaute genes grouped on ch-1 (1p34-35) — AGO3, AGO1, and AGO4, commonly known as transcription factors, if deleted, result in Wilms tumours and neuroectodermal tumours. Expression studies show they are involved in embryogenesis and development [45] HIWI, another Argonaute gene located at 12q24.33, is an orthologue of an Argonaute piwi gene found in Drosophila melanogaster [46]. It was unregulated in 12 of 19 testicular seminomas and is therefore associated with testicular germ-cell cancers, indicating their potential oncogenic behavior [47].

There are several genes in the process of cancer invasion and metastasis whose expression is regulated by miRNAs at the post-transcriptional level, including those that are involved in cell adhesion, in the epithelial–mesenchymal transition (EMT), in extracellular matrix (ECM) remodelling, in angiogenesis and in tumour–microenvironment interactions [48]. For instance, the tumour-promoting miR-21 is known to suppress tumour-suppressor pathways, while the miR-200 family inhibits EMT by targeting ZEB1 and ZEB2 and thus preventing E-cadherin-dependent epithelial adhesion [49].

miRNAs can also control ECM degradation and cellular migration by controlling matrix metalloproteinases (MMPs), integrins, and cytoskeletal signalling pathways. Further, EVs derived from tumour cells contain miRNAs that can be transferred to endothelial cells and stromal cells, inducing vascular permeability, angiogenesis, immune response, and the development of pre-metastatic niches [50]. For example, exosomal miR-105 targets the tight-junction protein ZO-1 in endothelial cells and promotes metastatic dissemination, while miR-210 is able to regulate the vascular signalling pathways and enhance angiogenesis [51]. The mechanisms are evidence that miRNAs modulate several steps of the metastatic process, including local invasion, intravasation and distant-colonisation of organs[52].Their functions,

however, are context-dependent, meaning that the same miRNAs can have multiple functions and opposing effects in different contexts of cancer, such as different types of cancer and microenvironments [53].

It has also been observed lately that genes coding for miRNAs are often spotted at fragile sites on mutational hotspots or at breakpoints that are frequently associated with cancer [54]. The miR17-92 cluster specifically indicates such an example; this cluster, located at an 800 bp region of C13orf25 (a non-coding gene), is composed of a series of miRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1) [55] This 800 bp non-coding segment is amplified in the majority of lymphomas, leading to overexpression of these miRNAs in lymphomas as well as solid tumors, indicating their oncogenic nature. However, another cluster of miRNAs, miR-15a/miR-16-1, occupying genomic position 13q14, is mapped to a 30-kb deleted segment between exons 2 and 5 of LEU2 (a non-coding gene), which is often repressed in patients with Chronic lymphocytic leukemia [56].

These are one of the many scenarios where miRNAs act as tumor suppressor genes in the latter case and oncogenes in the former case. miRNAs are notorious for their involvement in almost all developmental stages of cancer, from initiation to its proliferation and even metastasis. Figure 2 depicts the role of some miRNAs in the different stages of cancer development and onset.

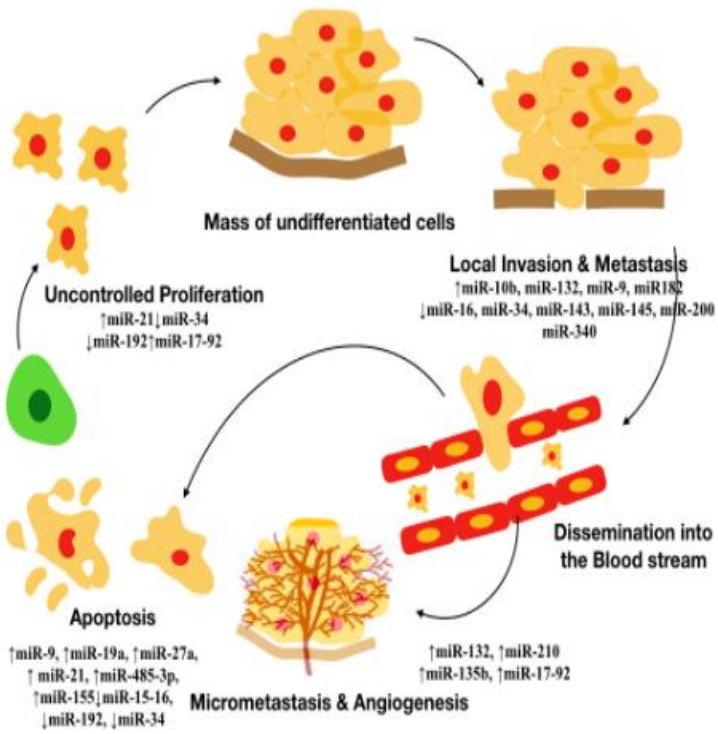

Figure 2. Known miRNAs and their potential role in Cancer development

This image has been created using the concept of [57] general layout of the working of miRNAs and the potential shortcomings in case of their absence, overexpression, or deletion has been depicted in Figure 3. So, depending on the part miRNA plays in cancer progression, different therapeutic approaches using miRNA to control cancer metastasis are categorized broadly as: (i) miRNA inhibition therapy in cases when overexpression of oncogenic miRNA is present, or (ii) miRNA replacement therapy when tumor suppressor miRNA is repressed. This can be achieved by delivering target miRNA using the conventional gene therapy approach or by specifically delivering miRNA to the target site[58] . Drawbacks of gene

therapy have made it obsolete, and so mostly nanocarrier-mediated delivery of miRNA is employed (Figure 3).

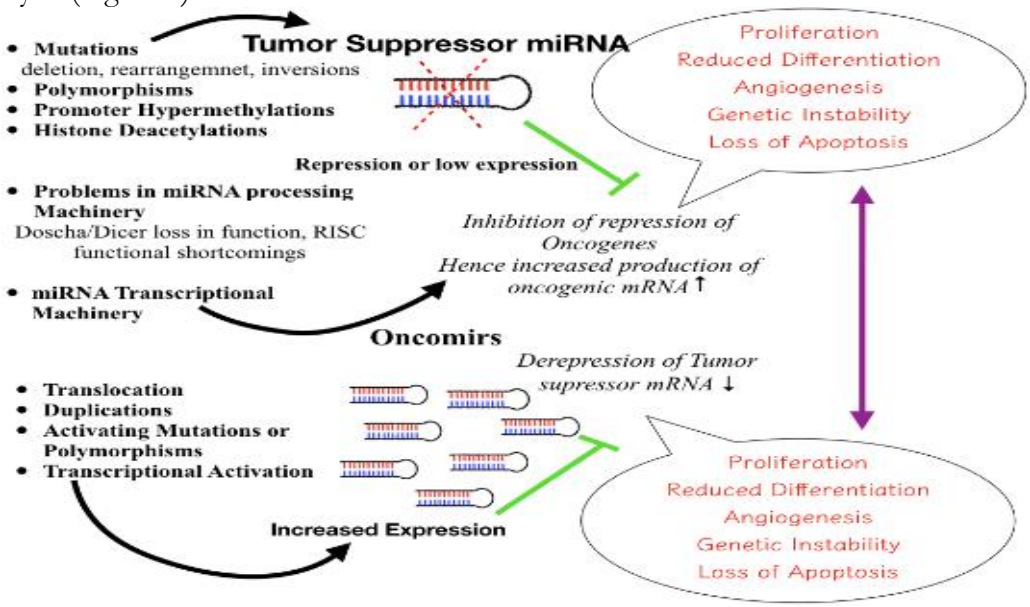

Figure 3. General layout of role of miRNAs in controlling cancer related genes (Tumor Suppressor Genes & Oncogenes)

Inhibition Therapy of Oncogenic miRNA:

Masking of a specific miRNA by using another molecule in order to block the binding of the first miRNA to the target messenger RNA (mRNA) without directly inhibiting the miRNA itself is an approach to therapeutic intervention [26]. In this method, a target-site blocker is a chemically modified antisense oligonucleotide that sterically blocks miRNA–Argonaute–containing RNA-induced silencing complex (RISC) interaction, by binding to the miRNA recognition sequence in the target mRNA. This means that the target mRNA is less likely to be targeted for translation inhibition or degradation by the miRNA, and that the expression of the target mRNA is restored or maintained [59].

Masking, on the other hand, prevents the miRNA from binding to the target transcript without affecting other target transcripts, unlike the direct inhibition of the miRNA as occurs in anti-miRNA therapy. Such specificity could present a possibility for the masking of miRNA, which could be used to restore expression of tumour-suppressor genes that are involved in cancer progression and metastasis [60]. In certain cancer types, upregulation of miRNA leads to disease pathogenesis, and in such cases, the best approach is to inhibit miRNA synthesis or activity by repressing the proteins that it activates [61].

The most frequently used repression therapy is by disrupting the miRNA-silencing complex. This is done by using anti-miRNA oligonucleotides (AMO) that prevent interaction between miRISC proteins and the microRNA or miRISC and its target mRNAs. This indirectly allows the tumor suppressor genes to be translated into their effector proteins by degrading the miRNA that degrades their respective mRNA. The AMOs selectively hybridize with their complementary miRNA and render them useless [62].

These are referred to as miR-MASKs and comprise single-stranded 2'-O-methyl-modified antisense oligonucleotides with sequences exactly complementary to the 3 ' UTR of the target mRNA [63]. Another approach can be masking the miRNA RISC binding sites by using complementary oligonucleotides that can prevent binding of miRNA to the 3 ' UTR of

mRNA, thus preventing the tumor suppressor mRNA from being translated and not degraded as would normally happen if the miRNA binding site were not masked [36].

Some other strategies to repress the activity of oncomirs are using miRNA sponges as a therapeutic strategy; they are competitive inhibitors of miRNA containing multiple complementary binding sites to miRNA in tandem and are transcribed in mammalian expression vectors [64]. The more miRNA target sequences, the more frequently these decoy transcripts will bind within a cell. The binding affinity of sponges to their target miRNA is enhanced by introducing a bulge that is cleaved off by Argonaute 2, so that stable interaction is maintained between miRNA sponges, ribonucleoprotein complexes, and their respective miRNA. This strategy led to the successful silencing of miRNAs. This strategy has been employed by Loya and her group for de-repression of miRNA in transgenic Drosophila in vivo, whereas Ebert et al. recently reported miRNA sponges for inhibition of miRNA in mammalian cells [65].

Another inhibition strategy is using small chemicals, drugs, or decoys that can regulate or modify the expression of target miRNAs by affecting the signalling pathways that are involved in the activation of transcription factors. These are responsible for activating miRNA-encoding genes or affecting the machinery that is involved in miRNA maturation and degradation. However, this approach requires a thorough screening of chemical libraries for identifying such chemical targets [66].

Replacement Therapy for Tumor suppressor miRNAs:

As the name suggests, this therapy helps in replacing lower levels of miRNA by using miRNA mimics that are oligonucleotide sequences similar to target miRNAs, usually double-stranded and sometimes chemically refashioned (modification of phosphor thiolate with 2'O-Me is often done) [67]. These miRNA mimics should efficiently perform the functions of the native miRNAs; they should be compatible with the RISC complex and regulate their target mRNAs. This strategy of replacing dysfunctional miRNA has been employed for the administration of cholesterol-conjugated miR-99a mimics intratumorally, with an efficient decrease in tumor growth observed in hepatocarcinoma-infected mice [68]. Ectopic expression of miRNA mimics has been found to induce cell death and obstruct cell multiplication. Restoration of miR-15-a and miR-29 using synthetic miRNA copies in prostate & AML cell lines has successfully induced cell death (apoptosis) [69].

A study reports an effective decrease in tumorigenicity in human rhabdomyosarcoma, liver, and AML xenograft murine models post treatment with intratumoral injection of synthetic miRNA-29 copies [70]However, no in vivo data suggest the same results using miRNA mimics that are delivered via intravenous injection. Pre-miRNA mimics (developed by Ambion) have also been introduced as a replacement therapy for miRNA. They need to be processed before activation, and their processing all occurs within the nucleus, so choosing the correct vehicle for their nuclear delivery is an important step influencing their success [71].

The goal of miRNA replacement therapy is to re-induce expression of miRNAs that are silenced in cancer cells using synthetic mimics of miRNAs, that are typically packaged into nanocarriers [72]. In cell-culture studies, miR-34a and miR-16 mimics have been found to have anti-oncogenic effects, such as the ability to block oncogenic signalling pathways, inhibit tumour-cell proliferation and regulate pathways involved in cancer progression [73]. Further investigation of this approach appears warranted, as delivery of miR-34a mimics in animal models, such as liposomal formulations, have shown anti-tumour effects and decreased tumour growth [74].

In human clinical studies, however, there are critical translation issues. MRX34 is a liposomal miR-34a mimic and yielded three partial responses in 66 patients who were evaluated in the Phase I trial, but the study was discontinued after serious adverse events that were immune-mediated killed four patients out of the 85 who were enrolled [75]. In another Phase I study, researchers tested the EGFR-targeted minicell delivery system containing miR-16 mimic in patients with recurrent malignant pleural mesothelioma [76]. Of 22 patients evaluated for response, one (5%) responded with a partial response, while 15 (68%) had stable disease, and dose-limiting toxicities were noted as well. All of these findings suggest that miRNA replacement has great experimental promise and has not yet been proven clinically. For clinical translation to be successful, tumour-specific delivery, immune-modulation, and dose and safety profiles need to be improved. Table 1, enlists a range of miRNAs involved in cancer treatment either as oncomirs or tumor suppressors.

Table 1. A List of miRNAs with their prospective part in Cancer development.

Phenotype/ Effect	miRNA	Gene locus	Cancer type	Biological function/Targets	Target genes	References
	miR-1	20q13.33	Prostate cancer, hepatocellular carcinoma, gastric cancer	mammalian heart development 9	ncRNA	[77]
TS/PM	miR-7	9q21.32	Colorectal cancer	Tumor suppressor	EGFR	[78]
PM	miR-9	1q22	Colorectal cancer, hepatocellular carcinoma	Inhibit the proliferative, migratory, and invasive capacities of NPC cells	CXCR4	[79]
OG	miR-10b	2q31.1	Solid tumors (breast, gliomas)	Encodes transcription factors	NF1, CDH1, ZEB1 & HOXD10	[80]
	miR-12b-1	11q24	Breast, lung, ovarian, cervical cancers	Involves transcription	STARD13	[81]
TG	miR-15	13q14.3	B-cell chronic lymphocytic leukaemia, prostate cancers	Induces Apoptosis,	BCL-2, CDC2, ETS1 and JUN	[82]
TG	miR-16	13q14.3	B-cell chronic lymphocytic leukaemia	Induces Apoptosis,	BCL-2, CDC2, ETS1 and JUN	[82]
	miR-20a	13q31.3	Prostate cancer	Has an anti-apoptotic role	E2F2	[83]
OG	miR-21	17q23.2	NSCLC, Glioblastoma, hepatocellular cancer, cervical cancer	Represses apoptosis, promotes growth	PDCD4, AP1, STAT3	[84]
TS	miR-34 family (miR-34a,	1p36 & 11q23	lung cancer, breast cancer	P-53 mediated apoptosis, metastasis	sirtuin 1 (SIRT1), BCL-2, CDK4, CDK6,	[85]

	miR-34b and miR-34c)				MET, Notch, MYC	
OG/TS	let-7	11q24	Lung Cancer	Cell proliferation	Repression of RAS, STAT3	[86]
OG-PM	miR-92a	13q31.3	Colorectal cancer, leukemia, hepatocellular cancer	Targets mRNAs corresponding to several proangiogenic proteins	PTEN	[87]
TS	miR-126	9q34.3	NSCLC, cervical cancer	Controls angiogenesis	VEGF-PI3K-Akt- MRP1, PTEN	[88]
TS	miR-124	8p23.1	NSCLC	Expression in neuronal cells	SOX8	[89]
PM	miR-137	1p21.3	NSCLC	Tumor suppressor	SLC22A18	[90]
TS	miR-181	1p37.5	Breast cancer	Differentiation of hematopoietic stem cells	BCL2	[91]
	miR-125b	11q24.1	Breast cancer	Potentiates macrophage activation	ERBB2	[92]
OG	miR-373	19q13.42	Human testicular germ cell tumors	Promotes cell proliferation and tumor development, mammalian pancreatic islet-cell development	p53-mediated CDK inhibition and suppression of LATS2	[93]
TSG	miR-143	5q32	Colorectal cancer	Regulation of mammalian adipocyte differentiation	KRAS, ERK5, VEGF, NFKB1	[94]
TSG	miR-145	5q32	Breast, colon, pancreatic and cervical cancer	Represses pluripotency in	MYC, MMPs, PLK 1, CDH2 & EGFR	[94]

				differentiating human ESCs		
OG	miR-155	21q21.3	Solid tumors (liver, lung Kidney, glioma), B-cell cancer, Burkitts & Hodgkins	Induces B-cell leucosis in chickens	Myc overexpression, SHIP, SP1, HDAC 4, HOA, SOCS1, SMAD2, SMAD5 & TP53INP1	[95]
	miR-196a	17q21.32	Colorectal cancer	Mammalian limb patterning	HOXB9, HOXB10	[96]
TSG	miR-200 family (miR-200a/b/429 and miR-200c/141)	Ch-1 & Ch-12	Solid tumors (breast, ovarian, lung)	Epithelial–mesenchymal transition (EMT)	ZAB1, ZEB2, BMI1, SUZ12, JAG1, SOX2, SP1, CDH1	[97]
OG	miR-221-222	X Chromosome	Solid tumors (liver, lung, pancreas)	Involved in induction of angiogenesis	CDKN1B, CDKN1C, BMF, RB1, WEE1, APAF1, ANXA1 & CTCF	[98]
	miR-17-92 cluster	13q31	Hepatocellular carcinomas, lymphomas	Polycistronic miRNA gene	C13orf25	[99]
OG	miR-372-373	19q13	Breast cancer & reproductive cancers	Modulates Wnt signaling pathway	LATS2	[100]
	miR1-2	18q11.2	Ovarian cancer	Differentiation of mesenchymal stem cells into cardiomyocytes	ncRNA	[101]
	miR-133 family	Ch-18, Ch-20 & Ch-6	Prostate cancer	Expressed in muscle tissue, regulation of	CASP9	[102]

	(miR-133a-1, miR-133a-2, miR-133b)			cardiomyocyte apoptosis		
	miR-122	18q21.31	Hepatocellular carcinoma	Expressed in mice liver function, used as a biomarker for hepatic conditions	CAT-1	[103]
TS	miR-132/212	Ch-11	Pancreatic cancer	Tumor suppressor	CyclinD1	[104]
TS	miR-335	7q32.2	Gastric cancer	Lymph-node metastasis	RASA1	[105]
OG	miR-374b-5p	Xq13.2	Gastro-intestinal cancers	Promotes gastric cancer cell invasion	RECK	[106]
TS-PM	miR-185	22q11.21	Colorectal cancer	Associated with the progression of CRC	STIM1	[107]
TS	miR-27a	19p13.12	Esophageal cancer	Inhibits cell proliferation	K-Ras	[108]
TS	miR-125a-5p	19q13.41	Glioblastoma	Promotes cell differentiation	TAZ	[109]
TS	miR-218	4p15.31	Prostate cancer	Represses TPD52 expression, increases cell apoptosis	TPD52	[110]
TS-DR	miR-873	9p21.1	Breast cancer	Regulates ERα transcriptional activity and tamoxifen resistance	ERα–CDK3	[111]

TS (Tumor Suppressor), OG (Oncogenic), PM (post metastatic), ncRNA (Nuclear RNA), TSG (Tumor Suppressor Gene), TS-DR (Tumor Suppressive Drug Resistant), TG (Tumor Growth)

Challenges in miRNA Delivery:

Like all other therapeutic approaches, miRNA therapy for controlling the development and prognosis of cancer faces various challenges that put a limit on its successful application for managing cancer [112]

The various barriers encountered are mentioned below:

Biological Instability:

miRNAs are short-lived with rapid degradation following endocytosis by a variety of nucleases. These endo- and exonucleases are simultaneously eliminated via the kidneys because of their low molecular masses, i.e., 1.3 k Da approximately [113]

Strategies to overcome the biological instability of miRNA and improve their in vivo half-lives, addition of certain molecular motifs, modification within the parent backbone and locking the nucleic acids have been developed, however, for the successful development of miRNA-based therapies in cancer, several other alternatives should be developed that can protect within the hostile environments without affecting their bioactivity [114]

Delivery Barriers and Safety Concerns:

In addition to biological instability, the therapeutic efficacy of microRNA (miRNA)-based cancer therapy is hindered by immune responses, off-target effects, inefficient endosomal escape, toxicity of the carriers, unfavorable biodistribution, and fast clearance [115]Therapeutic RNA or the delivery vehicle can lead to activation of innate immune pathways and induction of inflammation with dose limiting side effects. Off-target effects that disrupt normal gene expression can also lower the specificity of the treatment, resulting in undesired biological effects [116].

The inefficient endosomal escape mechanism leaves internalized miRNAs in endosomes and prevents their release into the cytoplasm and further incorporation into the RNA-induced silencing complex (RISC) [117]Additionally, cationic lipids and polymers can cause damage to the cell membrane and/or cellular stress, which can reduce cell viability [118]While some miRNA are able to penetrate the tumor, others remain in other organs, e.g. liver and spleen, which is not desirable, others are quickly cleared from the blood stream, and thus less circulation time and therapeutic miRNA to penetrate the tumour [119]

All these barriers reduce the engagement of the targets and the antitumor effect and increase the risk of toxicity. Thus, the design of biocompatible, tumour-targeted nanocarriers with the desired pharmacokinetic properties, efficient intracellular delivery and controlled release is crucial in improving the safety profile and therapeutic efficiency of miRNA based therapies for cancer [120]

Delivering the Cargo:

Transport of miRNA:

Another important point to focus on is the targeted delivery of the therapeutics, i.e., drugs, genes, in this case, miRNA [121]A lot of delivery vehicles have been employed over the decades, including adenoviral delivery systems, and non-viral delivery systems comprising synthetic materials like lipid-based delivery systems, i.e., liposomes and vesicles, etc. Synthetic materials have increasingly preferred over viral delivery systems due to simpler manufacturing, easier modification mechanisms, control of their size and the size of the cargo they carry, and most of all, decreased immunogenicity [122]

Synthetic materials are considered the vehicle of choice, especially for DNA, miRNAs & siRNA, because of their ability to condense negatively charged nucleic acid moieties via

strong electrostatic forces as they themselves are cationic. One problem faced using synthetic materials is their lowered efficiency in contrast to viral vector systems, but this has been greatly overcome by controlling the size of the synthetic particle and by actively targeting the carrier to the infected cell using target cell-specific receptors [123]In fact, nanotechnology and nanomaterials are the answer to many such queries.

One of the most basic oppositions faced for systemic transport of oligonucleotides like DNA or miRNA is their fragile nature and their vulnerability to degradation by endonuclease in the physiological environment and extracellular matrices [124]Naked RNA has a half-life of less than 5 minutes. In addition, the initial target of the siRNA or miRNA is always either the cytoplasm or the nucleus, where they have to function by modulating gene expression [125]So, the nucleotides have to cross all the kinetic barriers (blood, immune cells) and the physical barriers (cell membrane, nuclear membrane, etc.) to finally reach their destination. The stability of RNA in vivo can be enhanced, or its half-life can be increased by modifying the chemical structure of the RNA, i.e., by either exchanging the 2'-OH group on the ribose sugar with –F, –O–Me, or simple –H groups, or by modifying the RNA backbone with phosphorothioate [126]

Another strategy is to attach a cholesterol precursor to the 3' end of the sense strand that can help in preventing immature degradation of siRNA [127]All these problems can be addressed by the encapsulation of these poly-nucleic acids (DNA, siRNA, or miRNA) within a nano-particulate structure to provide them with their haven. They have additional advantages of not just protection against the hostile extracellular environment but also help increase the half-life of the cargo and their distribution to the target site. Many vectors have been used and then rejected over a span of many years, and many are under different stages of clinical trials; a list of all such nanocarriers is mentioned in Table 2. The following Figure 4 shows different vector types that are used in nano-based therapeutics. These include lipid vesicles, polymeric nanoparticles, gold nanoparticles, viral vectors, and porous nanoparticles functionalized with tumor-targeting peptides.

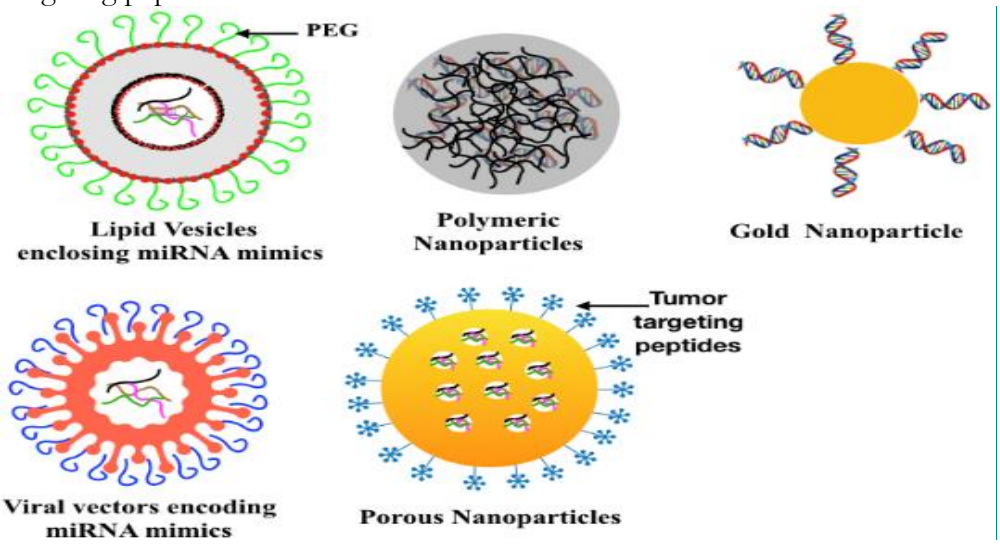

Figure 4. The different varieties of carriers used for in vivo delivery of miRNAs
The image has been based on the concept of figure [128]

Table 2. A brief overview of the different types of nano-carriers employed in miRNA Therapy

Vehicle	Type	Targeted miRNA	Cancer treated	Target genes	Effect	References
Viral Vectors	Lentiviruses	let-7g	Lung cancer	HMGA2	Proliferation, survival, and differentiation	[129]
		miR-15a-16-1	Prostate cancer	BCL2, MCL1, CCND1,	Promotes apoptotic cell death, represses tumorigenic growth in vitro and in vivo.	[130]
	Adeno-associated viruses	miR-26a	Liver cancer	GPBAR1	Suppresses tumorigenesis	[131]
Cationic NLC	Cationic liposomes	miR-34a	Lung cancer	PPARα	B16F10 melanoma lung metastasis	[132]
		miR-107	Head and neck squamous carcinoma	NF1	Represses tumor development in Head and Neck Squamous Cell Carcinomas	[133]
		miR-7	Colorectal cancer	EGFR	Tumor suppressor	[134]
		miR-101	Hepato-carcinoma	EZH2	Suppresses the malignant properties of hepatocellular carcinoma	[135]
Neutral NLC	Neutral lipid emulsion NLE	miR-124	Lung cancer	SOX8	Expression in neuronal cells	[136]
		let-7	Lung cancer	Repression of RAS, STAT3	Cell proliferation	[136]
		miR-34a	Lung & breast cancer	sirtuin 1 (SIRT1)	Diffuse large B-cell lymphoma	[137]

		miR-495	Lung cancer	PBX3	Induces apoptosis	[138]
Targeting-modified NLC	AEYLR	miRNA-125a-5p	Breast cancer	HER2	Promotes cell differentiation	[139]
		anti-miR-221	Hepato-carcinoma	PTEN, $P27^{kip1}$, and TIMP3	Gene silencing efficiency	[140]
Polymeric Nanocarriers	poly(amidoamine)	miR-21	Glioma	LRRFIP1, PTEN	Avoids immune destruction, sustains proliferative signalling	[141]
Inorganic nanoparticles	Silica nanoparticles	miR-155	Colorectal cancer	MIR155	Play a part in developmental functions of the cell, like growth and angiogenesis, etc.	[142]
	Gold nanoparticles	miR-145	Breast cancer, prostate cancer	MYC, CDH2 & EGFR	Down-regulates the junctional cell adhesion molecule	[143]
	Magnetic Nanoparticles	miRNA 221	Astrocytoma	MIRN221	Use as a cancer theragnostics probe	[144]

NLC (Nanostructured lipid Carriers):

The nanoparticle, after entering the body, penetrates the cells via different mechanisms. One of the most commonly employed entry mechanisms is receptor-mediated endocytosis [145]. The particle enclosing the miRNA enters the cell via engulfment and forms an endosome. This endosome escapes lysosomal degradation and unwraps, releasing the encapsulating miRNAs. The miRNAs, once released, are now free to perform their therapeutic role [146].

Viral Delivery of miRNAs:

Delivery of miRNA inside the living cell is similar to the delivery of genes and can be done via viral vectors [147]. miRNA antagonists or miRNA mimics encoded within viral vectors can be delivered inside living cells. Viral vectors are usually based on adenoviruses, lentiviruses, retroviruses, and adeno-associated viruses (AAVs). They encode miRNAs and allow safe delivery and efficient expression of target miRNAs to the target cells. Targeting of the diseased cell can be done by coupling tumor-specific ligands to the viral surface proteins (capsid proteins). miRNA-15a/16 were systemically delivered to the New Zealand Black (NZB) mouse model, a naturally available age-dependent animal prototype of chronic lymphocytic leukemia (CLL), using lentiviral vectors [148].

Delivery using these vectors was helpful in restoring the expression of miRNAs and preventing the chronic effects of CLL [128]. In myeloid-derived suppressor cells (MDSCs), TGF-β1 (tumor-inducing factor) induces miR-494 that causes pro-angiogenesis and metastasis in the tumor microenvironment. To address this, a lentiviral vector carrying a miRNA -494 antagonist was shown to significantly decrease the activity of MDSCs and prevent angiogenesis and, most importantly, metastasis in the murine breast cancer cells [149].

Drawback of using lentiviral vectors is the innate ability of lentiviruses to insert their own reverse transcribed DNA within the host genome that can lead to mutations and activation of oncogenic pathways. As a modification, non-integrating viral vectors like adenoviruses and AAVs are used, which, in contrast to lentiviruses, keep their DNA in episomal form within cells. AAVs were used in miRNA replacement therapy in liver cancer with promising effects. Systemically delivered miRNA-26a delivered via AAVs showed significant tumor inhibition by apoptosis and cell cycle arrest in HCC [150]. These and several other reports using viral vectors for the transfer of miRNA inside cancer cells indicate them to be a safe and sound route of particle delivery.

A major advancement in this field is the use of nanosized vesicles that are produced by viruses as cargo vehicles for miRNA therapy. It is reported the exploitation of viruses for packaging our respective miRNA and then further delivering it to target non-infected cells[58] This method showed enhanced efficacy and increased targeting efficacy. The use of viruses themselves or virus-released vesicles for targeted delivery has been restricted because of their immunogenic nature and their possibility it's been known for some replication competent retroviruses to cause CNS [151].

Another drawback of using viruses as delivery vehicles is their ability to insert their own genome within the cells, which might cause mutations that might lead to tumorigenesis. It seems attractive, but a lot of precision and refinement are required before its use for therapeutic purposes. The safer and more durable route employed by scientists is the use of non-viral nano-vectors, especially lipid-based systems [152].

Non-viral Lipid-Mediated Nanocarriers:

Lipid-based cargo delivery is one of the most widely used in vitro methods for the safe and efficient transfection of the cargo, but this method is rarely successful for iv vivo delivery of agents due to non-specificity, toxicity, and intolerance of the immune system [153]. Lipid-mediated siRNA transfection is almost 1000 times more effective than that when using naked siRNA. However, this problem can be resolved by using improved chemical structure and composition of the liposomes.

For example, PEGylation of liposomes has been found to improve their half-life from 6-10 hours in mice & almost 40 hours in human patients [154] Naked administration of apoB-specific siRNA showed no silencing of the target apoB mRNA in vivo, even at a dose response of greater than 50 mg/kg [155].

Whereas when liposome-mediated apoB anti-siRNA was administered, an almost 80% silencing was observed at minute doses of even 1 mg/kg [156] Wu and coworkers developed a lipolex enclosed cationic vector for the efficient delivery of miR-29b or miR-133b to treat non-small cell lung cancer (NSCLC), and the treatment was successful as it resulted in repression of target genes and their products CDK6, DNMT3B, and MCL-1. Similarly, a lipoplex-based cationic vector carrying a plasmid that expressed miR-7 helped in blocking tumor progression in an adenocarcinoma mouse model [157].

DDAB: cholesterol: TPGS/pre-miR-107 formulation led to a 45 % decrease in tumor growth on head and neck squamous cell carcinomas.

However, a major drawback of using Cationic lipids is their ability to bind to serum proteins, which not only increases their size, shortens their half-life in vivo, and increases non-specific interactions with target cells, but all this also leads to stimulation of the immune system and makes them prone to the reticuloendothelial system [158]Other than this, they are also notorious for toxicity within the body. Hence, there in vivo application becomes controversial. In replacement of this, anionic or neutral particle formulations have been prepared that are said to be more biocompatible than their cationic counterparts. Neutral lipids are mostly employed as "helper lipids" [159].

To increase the transfection capability and stability of the delivery vehicle, these include phospholipids like DOPE or cholesterol. Again, low efficacy, poor stability, and triggering of immune responses limit their use [147]. Addition of polyethylene glycol to the lipid formulations, however, helps to overcome the stability issue and also improves its pharmacokinetic profile. Here, PEG acts as an outer envelope encompassing the nucleic acids within a lipid core.

These surface modifications enhance particle stability with a prolonged blood circulation time of up to almost 72 h. PEG neutralizes the overall structure and charge of the complex and prevents it from interacting with the serum proteins and other blood cells. In this way, it helps in avoiding the immune activation via opsonisation and complement activation. An example of PEG coated

DOTAP: cholesterol: DSPE-PEG-OMe in 1:1:0.2 helped in inhibiting the progression of pancreatic tumors with miR-34a and miR-143/145 [160].

Polymeric Nano-Vector: Another class of delivery agents is the polymeric vectors that include:

Polyethyleneimines (PEIs):PEIs are synthetic cationic polymers with branched or linear structures of a variety of amine functional groups [161]The positive charge provided by the

amine groups allows these polymers to attach nucleic acids, hence forming an overall stable neutral structure with balanced charges [162]. They enter the cells via endocytosis, and cationic PEIs resist the acidic environment of the endosomes via their "proton sponge effect" buffering provided by the protonated polyethylenimines. This property helps the release of these polymers from the endosome back to the cytosol unscathed. These polymeric polyp lexes have been successfully reported in the delivery of miRNA in animal models. A 25 kDa PEI is considered a gold standard for gene transfection in vitro; however, it has several limitations, as with other non-viral delivery vehicles. They are clinically considered non-applicable due to their lethality, poor biodegradation, and, most importantly, poor efficiency when exposed to serum, resulting in non-specific binding [163].

However, biocompatibility issues can be overcome by manufacturing low-molecular-weight polyethyleneimines that are low molecular weight (LMW-PEI) [164]A comparison between LMW-PEI and high molecular weight PEI (HMW-PEI) carried out by Bieber and Elsasser showed that HMW-PEI was more damaging to the cellular membrane and posed a higher degree of toxicity than LMW-PEI. A plausible explanation for this might be less branching of LMW-PEI and differences in the charge density and degradability. LMW-PEI has been found efficient in delivering miR-145 and miR-33a mimics both locally and systemically in mice xenografts of colon cancer [165]The study showed that miR-145 increased apoptosis and inhibited tumor metastasis.

Atelocollagens

Atelocollagens are another naturally sourced cationic peptide that, due to their low toxicity, unnoticeable immunogenicity, and biodegradability, have been greatly employed to deliver target nucleic acids and oligonucleotides (siRNA & miRNA) [166]They are produced by treating type I Collagen with pepsin, which detaches amino- and carboxyl-terminal peptides responsible for its immunogenic behavior and allows the atelocollagen to exist at 4 °C in liquid form, while it is converted to a gel at 37 °C [167]. Atelocollagen interacts with oligonucleotides via electrostatic interactions.

These nano complexes facilitate cellular uptake and sustained delivery. After successful delivery of DNA and siRNA using atelocollagens were subsequently used in transporting miRNA, and for that purpose, miR-34a, which has the potential to initiate colon cancer and is involved in senescence, was used. After intratumoral injection of miR-34a mimics/atelocollagen nanoparticles in xenograft mice, a profound decrease in tumor was observed. Similarly, peritumoral injection of miR-135b inhibitor/atelocollagen complexes in lymphoma xenografts in mice repressed tumor development and maturation [168]

Successful suppression of gastric tumor metastasis was observed following treatment with miR-516a-3p/atelocollagen complexes. miR-16/atelocollagen mimics, when injected systemically in prostate xenografts in mice with bone metastasis, displayed a profound repression in tumor growth and metastasis with no apparent cytotoxic effects [167]These statistics indicate the potential of atelocollagen/miR nanocomplexes for cancer treatment.

Poly(lactide-co-glycolide) (PLGA) Nanoparticles:

These are water-insoluble polymeric nano-vectors with biomedical applications spanning more than 50 years. They gained importance because of their ability to entrap biologically active molecules and specifically protect entrapped nucleic acids from biological degradation, allowing easy manipulation and multiple structural modifications [169]These properties make them highly suitable for efficient microRNA therapy. Anti-miRNA-155

peptide nucleic acids (PNAs) were delivered using PLGA nanoparticles with an efficient therapeutic effect.

The particle surface was functionalized using penetratin, a cell surface penetrating peptide. They are also known for synthesizing MRI-detectable nanoparticles that were loaded with perfluoro-1,5-crown ether (PFCE) for 19F-MRI tracking. Their potential success lies in their high loading capacity, surface-tunable properties, and attachment of multiple cargoes simultaneously. However, certain limitations restrict their use; one drawback is their hydrophobicity and their ability to interact non-specifically with target cells. Although they protect encapsulated nucleic acids, their nucleic acid-loading technique can also degrade nucleic acids. PLGA hydrolysis can also damage nucleic acids due to the acidic microenvironment.

Liposome-Hyaluronic Acid (LPH) Nanoparticles:

Another class of lipid nano-carrier system is polycationic-liposome-hyaluronic acid (LPH) nano-vectors [170]They reportedly co-transported siRNA and miRNA-34a to a metastasized B16F10 melanoma lung model using LPH nanoparticles modified with the GC4 single-chain antibody fragment specific for tumor cells. The siRNA targeted gene products of c-Myc, MDM2 & VEGF, whereas miR-34a inhibited and reduced tumorous growth to almost 20 % compared to untreated cells [171]

This system helps in the co-administration of both miRNA & siRNA, allowing a synergistic therapeutic effect. LPH nanoparticles coupled with an integrin-binding tripeptide (cyclin-RGD) (cRGD-LPH) successfully transported anti-miR-296 and effectively prevented angiogenesis and tumor endothelial cell migration. The study was conducted in endothelial cells of the human umbilical vein model by targeted uptake via αvβ3integrin [172]

Dendrimers:

Another class of synthetic nano vehicles for miRNA delivery is dendrimers. They have attracted considerable attention over the years due to their high aspect ratios. Their positive charge enables them to form complexes with negatively charged nucleic acids, thereby facilitating the delivery of miRNA and siRNA. A poly (amido)amine (PAMAM) dendrimer was used to deliver an anti-miR-21 complexed with 5-fluorouracil to glioblastoma cells [173]This PAMAM dendrimer is less than 100 nm in size. This anti-miR-21 renders previously resistant glioblastoma cells sensitive to Taxol chemotherapy by downregulating STAT3 and p-STAT3 [174]

A major drawback of dendrimers for miRNA delivery is that increasing the generation number makes them highly toxic. Most of the injected PAMAM dendrimer accumulates in the liver, leading to liver damage and disruption of glucose metabolism. This, however, can be mitigated to some extent by shielding their surface charge via PEGylation or conjugation with lauroyl chains, which results in decreased toxicity [175]Another drawback is their non-specific delivery mechanism. For the application of dendrimers as anticipated and sought-after transfecting agents, necessary structural modifications are needed to overcome their drawbacks.

Inorganic Materials:

Metallic nanoparticles and their oxides fall under this category of inorganic delivery vehicles that broadly include nano-gold complexes, nano-diamonds, silica, and iron oxide nanoparticles. Gold nanoparticles are readily involved as miRNA or siRNA transporters due to their amazing optical properties, and easily tunable surface chemistry via the addition of

thiols, PEG, or amino groups [176]A miRNA-AuNP complex (miRNA-130b) labeled with Cyanine-5 was delivered to myeloma cells, and it efficiently down-regulated oncogenic gene expression. Another group used PEG-thiol functionalized gold nanoparticles for delivering miRNA to cancer cells. This unmodified miR-AuNP-S-PEG complex exhibited high loading capacity, improved stability (half-life), decreased cytotoxicity, and increased fold transfection capability compared with the gold nanoparticle polyelectrolyte complex and Lipofectamine [177]

A gold nanoparticle complexed to RNAi and antisense oligonucleotide was able to successfully deliver anti-miR-29b inside HeLa cells. Post-treatment showed enhanced apoptosis and an increase in levels of MCL-1 protein. Another class of inorganic nanoparticles is magnetic nanoparticles; their success lies in their ability to selectively target tumor cells using their internal magnetic fields. They have been extensively used for targeted nucleic acid delivery as their use limits the risk of biocompatibility. Zinc-doped iron oxide nano-vectors have been used successfully for the delivery of let-7a miRNA to glioblastoma brain cell model systems. The paper reports MNP-mediated delivery of Let-7a that induces apoptosis by specifically targeting heat shock protein-mediated multiple key pathways like cell survival and repairing DNA using IGF1R & RAS pathways. Anti-miR-10b has been successfully delivered using magnetic nanoparticles, and it reduced and inhibited metastasis of breast cancer cells to lymph nodes, suggesting their potential for treatment of metastatic cancer [178]

Modern Nanocells (Dream vectors):

A major advancement in the field of nanovectors is the use of bacterially derived nanocells, which are almost 400 nm sized small vesicles that have been employed for miRNA delivery. Before this, they have been used for the transfection of chemotherapeutic drugs and targeted to cells using antibodies [179] An EnGeneIC delivery vehicle (EDV) is produced when a genetically modified bacterium divides at two division forks, centrally and terminally; the part of the divided cell that lacks the genome is used as a delivery vehicle. These empty nanocells are then loaded with drugs or miRNA and delivered specifically to the target cells. Targeting can be achieved using cell-specific recognition peptides, as in traditional methods. Another phenomenon unique to nanocells is their passive targeting of tumor cells.

This is achieved by their large size (400 nm ± 20 nm), which enables them to enter tumor vasculature due to its leaky nature, and, in this way, we can easily target them to receptors present on normal cells but abundant on cancer cells (http://engeneic.com/edv-technology/). TargomiRs and mesomiR-1 [180], these are nanocells undergoing phase 1 clinical trials for miRNA therapy to treat glioblastomas, mesothelioma, and other solid tumors. Many therapeutic miRNA mimics loaded onto EDV nanocells are currently in clinical trials, with encouraging results. The clinical trials of miRNA-based nanotherapeutics have proved that delivery of regulatory RNA molecules for clinical use is achievable, but is still limited to early stages. TargomiRs (MesomiR-1), an EGFR-targeted minicell platform, have entered into a first-in-human Phase I clinical trial in patients with advanced non-small-cell lung cancer (NSCLC) and recurrent malignant pleural mesothelioma (MPM) [181]

The study showed preliminary anti-tumour activity, but failed to define the clinical efficacy and to initiate a valid Phase II programme. Other candidates have experienced important translation barriers: MRX34, a liposomal miR-34a mimic, was discontinued due to severe immune-mediated toxicities and treatment-associated deaths, while INT-1B3, a lipid nanoparticle formulation of a miR-193a-3p mimic, was discontinued in early clinical

development, citing lack of funding as the reason [182]But Cobomarsen, an inhibitor of the oncogenic miR-155, also missed a progression milestone when its Phase II programme ended due to business considerations. TTX-MC138 is a clinical-stage investigational product that carries an anti-miR-10b agent, with an iron-oxide nanoparticle [183].

Taken together, these programmes provide a demonstration of the potential targeting capabilities of nanocarriers in combination with miRNA and the difficulties to achieve tumour-specific distribution, the efficient delivery to the cell interior, to ensure immune safety, and to reproduce a therapeutic effect [184]. The examples listed here do not constitute an approved miRNA based nanotherapy for cancer, so care needs to be taken distinguishing clinical data from promising preclinical data as of October 2026 [185]

Comparative Evaluation of miRNA Delivery Platforms:

The ability of the delivery system to protect RNA cargo, promote cellular uptake and endosomal escape, direct the RNA to the tumour site and reduce toxicity are all key factors in the therapeutic efficacy of microRNA (miRNA) delivery systems [186]There are efficient viral vectors such as adenoviral, adeno-associated viral, and lentiviral vectors that can also deliver the encoded RNA for a longer period of time. However, the use of these in the clinic might be limited due to immunogenicity, pre-existing immunity, the cargo capacity in some vectors, the complexity of manufacturing, and, in the case of integrating vectors, by the risk of insertional mutagenesis [187]

Furthermore, the viral vectors that deliver miRNA precursors are mechanistically different from those that deliver synthetic miRNA mimics directly and sustained expression may not be desirable in certain situations where measures of dose control are critical to success [188]Lipid-based nanocarriers (LNPs) and liposomes are used to encapsulate miRNAs and shield them from nuclease degradation and to enhance cellular uptake. Ionizable lipids may also enable endosomal escape by interacting with the endosomal membranes, leading to more miRNA available in the cytoplasm to enter into the RNA-induced silencing complex (RISC)[189]. Among the more clinically advanced RNA-delivery systems are lipid-based platforms, which can be easily formulated and have well-developed manufacturing technologies [190]

However, there are several concerns such as accumulation in the liver and spleen, activation of complement, inflammatory responses, lack of penetration into solid tumours, and potential toxicity after repeated dosing [191]Among the polymeric nanocarriers that provide tunable physicochemical properties, protection of RNA cargo, surface functionalization, and controlled or stimulus-responsive release are polyethy lenimine (PEI), poly(lactic-co-glycolic acid) (PLGA), chitosan, and dendrimers [192]

Cationic polymers can facilitate nucleics complexation and escape from the endosome, but if there is too much positive charge, they could damage the membrane, exert cytotoxicity, and interact with serum proteins non-specifically [193]The biodegradability can be used to enhance tolerability, but the degradation kinetics, cargo-release profile, and manufacture reproducibility needs to be optimized. The inorganic nanocarriers (golds, silica, iron oxide, calcium phosphate) can have meaningful surface chemistry to adjust and offer a high loading capacity, imaging function, or stimulus responsiveness, depending on the composition [194]Under acidic intracellular environment, calcium phosphate might dissolve, while the gold and silica systems might be structurally stable and provide versatile surface modification [195]

The biodegradation and clearance are, however, quite different in various materials, and systemic use may be restricted by persistent accumulation or organ toxicity, as well as by uncertainty about the safety of long-term use. Active targeting with antibodies, peptides or aptamers or other ligands may facilitate the cellular recognition of these platforms, but it does not always mean that they are able to penetrate the tumour and deliver them in the cytoplasm [196]Likewise, the enhanced permeability and retention effect for passive targeting is very different between tumour types and patients. In summary, lipid-based systems are the more mature option for clinical translation while polymeric and inorganic systems offer opportunities for customisable delivery, but are still to be well characterised in terms of safety, biodistribution and manufacturing consistency [197]

Although viral vectors will not be appropriate for all applications of gene transfer, they do have some applications for which they are considered useful, and must be carefully evaluated for immune responses and duration of expression [198]Thus, the best platform should be chosen based on the therapeutic miRNA, tumour biology, route of administration, duration of activity, targeting specificity and safety parameters. Before moving forward with promising systems into human trials, future development should focus on standardizing delivery efficiency, endosomal escape, tumour accumulation, off-target gene regulation, pharmacokinetics and toxicity of systems in clinically relevant models [199].

Unresolved Challenges and Emerging Solutions in miRNA Delivery:

Although there have been significant improvements made in terms of miRNA-based cancer treatment, effective and selective delivery to the cancerous sites still represents one of the biggest obstacles [186]. Indeed, therapeutic miRNAs may be vulnerable to nucleases, fast clearance from the bloodstream, insufficient accumulation in tumors, inefficient delivery to the cells, sequestration in endosomes, and regulation of several targets leading to non-specific effects [200]These issues are also hampered by tumor and metastasis heterogeneity, rendering ineffective the use of passive delivery based on the enhanced permeability and retention effect [201]Potential strategies that include chemically modified miRNAs, ionizable lipid-based nanoparticles, ligand-targeted or biomimetic nanocarriers, engineered extracellular vesicles, hybrid nanoparticles, and pH- or redox-responsive drug delivery systems could increase the stability, tumor specificity, intracellular delivery, and safety of the miRNA-based therapeutics [202]

On the other hand, the application of artificial intelligence for the development of novel nanoparticles, biomarkers for patient selection, and personalized miRNA profiling could help optimize the delivery systems for the improved efficacy [203]Nevertheless, challenges such as reproducibility of the nanoparticle synthesis, batch-to-batch variability, safety/toxicity, pharmacokinetics, and standardization of the technology are still open questions. Future investigations should, therefore, focus on the biodistribution, tumor penetration, target interaction, and safety studies [204]MicroRNA (miRNA) nanotherapeutics have progressed from ionizable lipid nanoparticles (LNPs), ligand-functionalized carriers, biodegradable polymers and extracellular vesicles (EVs), to stimuli-responsive nanomaterials [205]However, there are still some obstacles to their translation in the clinic. Chemical modification, protective encapsulation, and surface shielding of the biological instability and rapid clearance is being addressed, while preserving the activity of miRNAs and avoiding unwanted recognition by the immune system [206]Two major drawbacks are still tumour accumulation and heterogeneous

penetration, due to the spatial heterogeneity of the tumour microenvironment, stromal density and tumour vascularity [207]

While the selectivity may be improved by targeting via a ligand, biomimetic carriers or microenvironment-responsive systems, uniform tumour penetration does not guarantee enhanced cellular uptake. One of the other major drawbacks is that internalized miRNAs are unable to escape from the endosome to interact with the RNA induced silencing complex (RISC) [208]Solutions exist such as ionizable lipids, fusogenic materials and pH-responsive polymers, but these materials need to be standardized for performance and safety. In addition, miRNAs mediate the repression of many transcripts, and the potential for off-target gene repression, context-dependent effects and unintended immune activation are major safety considerations [209]

All of these risks emphasize the need for long-term toxicological evaluation and dose optimization, as well as transcriptome-wide profiling. The beneficial aspects of the emerging EV-based and hybrid carriers include enhanced biological compatibility, and the use of AI for formulation design may help shorten the time required for optimization of the composition and delivery properties of the carrier; however, issues of reproducibility, loading efficiency, scale up and quality control have yet to be resolved [210]

Future Prospects:

The use of nanocarriers is the most attractive option for targeting cancer cells and delivering miRNAs. Their ability to specifically target complementary mRNA allows us to either inhibit oncogene expression or increase expression of tumor suppressor genes by targeting miRNAs that splice tumor suppressor mRNAs. Their association in regulating the different stages of cancer development, initiation, proliferation, angiogenesis, and, most importantly, metastasis makes them highly relevant therapeutic targets. However, their potential can be exploited only once they are delivered to their respective tissues within the body, a process enabled by nanoscale vehicles.

These vehicles not only deliver the target miRNA but also protect it from the dangers of the in vivo microenvironment and transfer it to the target tissue. Nanocarriers have been preferred over microcarriers because of their extremely small size, which makes them highly penetrant, and their biocompatible nature, which may improve biocompatibility, although toxicity remains a concern. However, all is not well, as the cytotoxicity issue continues to prevail and limit their use. Work has been abundant on the targeted delivery of RNAi, but eventually the results are not absolute; moreover, the pressing query is where does the carrier go once it has delivered its cargo, biodistribution of the miRNA, dose level, and evasion of the carrier from the immune system. All of these questions must be addressed before their application to human subjects.

Systemic delivery of cationic lipids has been known to cause charge-dependent toxicity; however, this can be mitigated by masking surface charges with neutral molecules, such as PEG, or, more precisely, by using a biodegradable system. Another important factor affecting the overall efficacy of miRNA therapy is the use of non-targeted carriers. The urgent need is to use recognition peptides, aptamers, antibodies, and ligands specific for target-cell receptors to deliver carrier molecules to their respective cancer cells selectively. This will help address non-specificity issues that are critical in cancer therapy. The biological uptake of miRNA is as important as its biodistribution and stability. By-passing physiological barriers is the key obstacle to the success rate of miRNA therapy.

Using penetrating peptides, such as transferrin, appears to enhance uptake; however, the blood-brain barrier limits the use of miRNA therapy in brain tumor treatment in vivo. MRX34 is a ds-miRNA mimic introduced by Mirna Therapeutics that is a combination of Lipid Nanoparticle Smarticles (LNPs) and mir-34 mimics [211]for the treatment of multiple solid tumors like hepatocellular carcinoma and liver metastasis. The therapy was terminated during phase I clinical trials [212]Another breakthrough is the use of EnGeneIC's bacterially-derived EDV™ nanocell (EnGeneIC Dream Vector) as a delivery vector for miRNA. This EDV™ nanocell is in the dose-finding phase I clinical trial [212]

This EDV is loaded with a miR-16 mimic and co-loaded with an anti-epidermal growth factor to target tumor cells. The therapy demonstrated promising antitumor activity in 22 patients evaluated. The use of this nanocell is a way forward in nanocarriers with efficient targeting due to their small size (200-400 nm) +/- 20 nm [213]Another EnGeneIC's EDV™ nanocell is under phase I clinical trials for the treatment of Glioblastoma Multiforme. MesomiR-1, developed by EnGeneIC, is a miR-16 mimic encapsulated within the EnGeneIC delivery vehicle (EDV) nanocell and has been employed for the treatment of Mesothelioma and non-small cell lung cancer, with Phase I clinical trials ongoing [214][215]The use of these nanocarriers has revolutionized miRNA therapy, with success rates increasing and promising results. Research organizations and biotechnology companies are making breakthroughs in the field.

Major companies such as EnGeneIC, miRagen Therapeutics, Mirna Therapeutics, Regulus Therapeutics, Santaris Pharma A/S, and Hoffmann-La Roche are engaged in advanced research and have products in preclinical and clinical trials. The road to miRNA therapy using nanovectors is challenging, but it holds significant potential and, over the coming years, will yield an efficient and effective cargo vesicle with cancer- and tumor-eradicating capacity. The development of new technologies such as ionizable lipid nanoparticles (LNPs), polymeric carriers, extracellular vesicles (EVs), and stimuli-responsive nanocarriers have developed new methods to enhance miRNA stability, cellular uptake, and tumour targeting [202]

Nevertheless, endosomal escape remains inefficient, there are off target effects, immune responses, heterogeneous tumour penetration and carrier toxicity remains to be a problem for clinical translation [216]. Novel carriers with high cytoplasmic penetration and good biocompatibility, targeting and controlled delivery of the miRNAs are recommended for further studies. Further optimization of delivery using AI assistance for formulation design and hybrid nanocarriers is possible, but needs to be tested experimentally [217]

There are several gaps in the research that warrant more attention: the absence of standard delivery assays, limited validation in clinically relevant metastatic models, lack of long-term safety data and scalable manufacturing challenges [204]Comparative studies, a thorough toxicological evaluation, and clinically designed trials are crucial to overcome these restrictions and advance the translation of intriguing preclinical results into safe and effective miRNA-based cancer treatments [216]

Conclusion:

MicroRNAs (miRNAs) are new players in the landscape of genes regulating gene expression after transcription and are promising therapeutic agents for controlling the metastasis of cancer. They can simultaneously target several molecular pathways implicated in tumour proliferation, apoptosis, epithelial–mesenchymal transition (EMT), extracellular

matrix remodelling, angiogenesis, invasion, migration and metastatic colonization, providing a unique therapeutic benefit. Dysregulated miRNAs can be either Oncogenic miRNAs (oncomiRs) or Tumour Suppressive miRNAs which suggest therapeutic inhibition of overexpressed oncomiRs and replacement of downregulated tumour-suppressive miRNAs. However, because of the complexity of miRNA-mediated gene regulation, it is important to account for tumour-specific molecular profiles, context, and the possibility of pleiotropic effects of potential simultaneous modulation of multiple target genes.

Nanotechnology has broadened the therapeutic potential of miRNA-based therapies by offering delivery platforms which are able to deliver RNA cargo to cells without degradation by enzymes, enhance cellular uptake, and mediate intracellular transport of the RNA. Lipid nanoparticles, liposomes, polymeric nanocarriers, inorganic nanoparticles, extracellular vesicles and engineered minicell based systems have different advantages in cargo protection, functionalization of the nanoparticle surface, controlled delivery and potential targeting to tumour. But, so far no single delivery platform has been able to conquer all significant biological and technological hurdles.

Rapid systemic clearance, heterogeneous tumour accumulation, lack of penetration into metastatic lesions, poor endosomal escape, off target gene regulation, and carrier-associated toxicity remain to be major challenges for therapeutic effectiveness. In addition, the higher the uptake, the less likely it is to be effectively delivered to the cytoplasm and to interact with the desired target miRNA. Clinical trials have shown the feasibility of miRNA based therapeutics in humans, but also important translation barriers have been observed. Despite severe immune-mediated adverse events that led to the discontinuation of MRX34, the liposomal miR-34a mimic, the need to perform extensive safety testing is highlighted, whereas the results from the Phase I trials of TargomiRs demonstrate the potential and the limitations of minicell-mediated miRNA delivery. Such experiences have shown that beneficial preclinical effects cannot be translated to clinical benefit. Therefore, further development should include comprehensive pharmacokinetics, biodistribution, target engagement, innate immune activation, off-target and long-term toxicity evaluation as well as thorough assessment of therapeutic efficacy. Future research should focus on the development of biocompatible, biodegradable and scalable nanocarriers, which have better endosomal escape and selective delivery to primary tumours and metastatic sites.

The development of a combination of tumour-specific miRNA signatures, validated predictive biomarkers, transcriptomic analysis, and computational tools may help to choose the right therapeutic miRNA and delivery system. Besides, patient-derived organoids, orthotopic tumour models and clinically relevant metastatic models should be employed to test therapeutic efficacy in more humanistic setting.

Characterization protocols, manufacturing processes, potency assays and clinical trials will also need to be standardized, reproducible, validated, and well-designed to achieve greater comparability among studies and facilitate regulatory evaluation. All in all, there is great potential for the fields of miRNA biology and nanomedicine to be combined to create more targeted therapies for cancer metastasis. The successful clinical translation will, however, require the optimization of delivery efficiency, as well as tumour selectivity, predictable biological activity, acceptable safety and reproducible therapeutic benefit. Combined therapy with miRNA nanotherapeutics might prove to be viable drug strategies in the clinic, either as single drugs or as drug combinations that would be specific for the molecular profiles of

different tumors. They require more extensive preclinical and clinical testing before they can be widely used in treatment.

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