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REVIEW

# Targeting Oncogenic miRNAs in NSCLC: Therapeutic Strategies and Emerging Approaches

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**Abstract:** Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related deaths globally, with poor prognosis in advanced stages despite therapeutic advances. MicroRNAs (miRNAs) play a critical role in NSCLC pathogenesis, acting as tumor suppressors or oncogenes (oncomiRs), regulating key pathways involved in cancer progression and drug resistance. This review explores various therapeutic strategies targeting oncogenic miRNAs in NSCLC, with a particular focus on small molecule inhibitors (SMIs). SMIs offer potential advantages over RNA-based therapies, such as better pharmacokinetics and oral bioavailability, though direct evidence for SMIs targeting oncogenic miRNAs in NSCLC remains limited. The review examines current research on SMIs, miRNA mimics, antisense oligonucleotides, and other approaches, while discussing the challenges and opportunities for clinical translation. It concludes that while miRNA-based therapies are promising, substantial research is needed to develop effective and selective small molecule inhibitors for NSCLC treatment.

**Keywords:** small molecule, microRNA, NSCLC, exosomes

## Introduction

Lung cancer remains a formidable global health challenge, standing as the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) constitutes the vast majority, approximately 80–85%, of all lung cancer diagnoses. Despite significant advancements in diagnostic techniques, surgical interventions, chemotherapy, and the advent of molecular targeted therapies, the prognosis for NSCLC, particularly in advanced stages, remains relatively poor, with a 5-year relative survival rate hovering around 20%.[1,2] This underscores the urgent need for novel therapeutic strategies that can overcome inherent or acquired drug resistance and minimize off-target effects, issues that often compromise the efficacy of current treatment modalities.[3] In particular, the need for targeted therapies that can address resistance mechanisms in NSCLC remains one of the key challenges.

The development of targeted therapies, such as tyrosine kinase inhibitors (TKIs) directed against specific mutations like EGFR and ALK, has undoubtedly improved outcomes for select patient populations, deepening our understanding of NSCLC biology and paving the way for personalized medicine approaches.[2,4] However, the emergence of resistance to these targeted agents, exemplified by acquired resistance to EGFR-TKIs like gefitinib, presents a major clinical hurdle.[4,5] Therefore, alternative therapeutic strategies that can bypass these resistance mechanisms, such as miRNA modulation, are being increasingly explored.

In recent decades, the landscape of cancer research has been significantly reshaped by the growing understanding of the intricate roles played by non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), in regulating gene expression and cellular processes critical for cancer initiation, progression, metastasis, drug resistance, and immune evasion.[1,3,6] MiRNAs are small, endogenous, non-coding RNA molecules, typically 19–25 nucleotides in length, that function as post-transcriptional regulators by binding to complementary sequences, primarily in the 3' untranslated regions (3'UTRs) of target messenger RNAs (mRNAs). This binding leads to either translational repression or degradation of the target mRNA, thereby modulating protein expression.[7,8] The multi-step process of miRNA biogenesis and its druggable checkpoints are summarized (Figure 1). Dysregulation of miRNA expression is a hallmark of NSCLC and is

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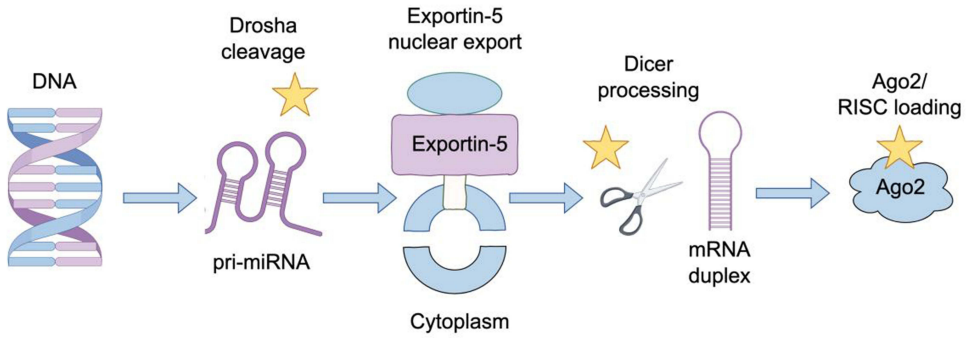


**Figure 1** Schematic of miRNA Biogenesis and Its Druggable Checkpoints. This figure illustrates the multi-step process of miRNA biogenesis, from the transcription of primary miRNA (pri-miRNA) to the processing of precursor miRNA (pre-miRNA) and its eventual incorporation into the RNA-induced silencing complex (RISC). Key molecules involved in this process include Drosha, which cleaves pri-miRNA into pre-miRNA in the nucleus; Dicer, which processes pre-miRNA into mature miRNA in the cytoplasm; Exportin-5, responsible for exporting pre-miRNA from the nucleus to the cytoplasm; and Ago2, the core component of the RISC complex, which facilitates the degradation or translational repression of target mRNAs. These molecular participants play crucial roles in miRNA maturation and function, making them potential targets for therapeutic intervention.

closely associated with various aspects of the disease, including cell proliferation, apoptosis, migration, invasion, angiogenesis, stemness, and sensitivity to therapy.[9,10] MiRNAs can act as either tumor suppressors (often downregulated in cancer) or oncogenes (oncomiRs, often upregulated in cancer), depending on their target genes and the cellular context.[6,11] The aberrant miRNA signature observed in NSCLC tissues and cell lines highlights their potential as diagnostic biomarkers and, more importantly, as promising therapeutic targets.[1,6]

Given their central regulatory roles and frequent dysregulation in NSCLC, miRNAs represent attractive candidates for therapeutic intervention. Strategies broadly fall into two categories: restoring the function of downregulated tumor-suppressor miRNAs (using miRNA mimics) or inhibiting the activity of upregulated oncogenic miRNAs (using anti-miRNAs or inhibitors).[3,6] In addition to RNA-based therapies, there is growing interest in SMIs as a means to modulate miRNA activity. Small molecule inhibitors are low-molecular-weight compounds (typically < 1000 Da) that can modulate biological processes by directly binding to RNA or protein targets involved in miRNA biogenesis and function. They are generally classified based on their mode of action, including those that inhibit miRNA transcription, processing enzymes (such as Drosha or Dicer), or miRNA–mRNA interactions. Compared with RNA-based therapies, SMIs possess several favorable characteristics, such as high chemical stability, well-defined pharmacokinetics, and the potential for oral administration. Their small size facilitates cellular permeability and systemic distribution, offering practical advantages for therapeutic delivery and clinical translation. While RNA-based approaches utilizing synthetic miRNA mimics or antisense oligonucleotides (anti-miRs) have shown promise in preclinical studies, their clinical translation faces significant challenges, primarily related to effective and safe delivery to tumor sites, stability in biological fluids, and potential off-target effects.[3,12–14] This has spurred interest in alternative approaches, including the potential use of small molecule inhibitors to modulate miRNA activity or expression. The concept of using small, drug-like molecules to target specific RNA structures or the proteins involved in miRNA biogenesis, processing, or function offers a distinct therapeutic avenue that could potentially leverage established drug development pipelines and delivery mechanisms compared to oligonucleotide-based therapies. This review aims to explore the potential of targeting oncogenic miRNAs in NSCLC using small molecule inhibitors, examining the underlying mechanisms, current advances, and translational opportunities. However, it is important to note upfront that the provided literature, while extensively covering the roles of miRNAs in NSCLC and various RNA-based therapeutic strategies, contains limited direct information specifically on small molecule inhibitors designed to target oncogenic miRNAs. The subsequent discussion will therefore integrate the available information on miRNA mechanisms and therapeutic approaches from the provided sources, highlighting the context and potential relevance to the small molecule inhibitor concept, while also acknowledging the current gaps in the literature specifically addressing this precise strategy.

The study of miRNAs in NSCLC has revealed their multifaceted involvement in nearly every aspect of cancer biology, from initial transformation to metastasis and therapeutic response. The provided literature underscores the

critical roles of specific miRNAs, the complex regulatory networks they participate in, and various strategies being explored to therapeutically modulate their activity. While the core focus of this review is on therapeutic strategies targeting oncogenic miRNAs in NSCLC, the existing studies primarily focus on the broader mechanisms of miRNA dysregulation and the development of RNA-based therapies, providing important context and identifying key targets and pathways that could inform the development of future small molecule interventions.

## microRNAs in Non-Small Cell Lung Cancer: Functional Roles and Therapeutic Targets

Widespread dysregulation of miRNA expression occurs in NSCLC compared to normal lung tissue, with specific miRNAs acting as either tumor suppressors or oncomiRs (Figure 2).[15]

These aberrant expression profiles are intimately linked to the hallmarks of cancer. For instance, miR-20a-5p is reported to be significantly upregulated in NSCLC tissues and cell lines, with higher levels correlating with larger tumor size and lymphatic metastasis.[16] Functional studies demonstrated that overexpression of miR-20a-5p enhances the viability, cell cycle progression (increasing the ratio of cells in S phase), and invasiveness of NSCLC cells. Conversely, knockdown of miR-20a-5p inhibits these aggressive cellular behaviors.[17] Mechanistically, miR-20a-5p exerts its oncogenic effects by directly targeting and downregulating KLF9 (Kruppel-like factor 9), a transcription factor known to have tumor suppressor functions in various cancers (Figure 3).[16] The negative correlation observed between miR-20a-5p and KLF9 expression levels in NSCLC tissues further supports this regulatory axis. Importantly, restoring KLF9 expression was shown to reverse the pro-proliferative and pro-invasive effects induced by miR-20a-5p overexpression, confirming KLF9 as a key downstream mediator of miR-20a-5p's oncogenic activity in NSCLC.[16] The miR-20a-5p–KLF9 regulatory axis promotes malignant phenotypes in NSCLC.

This identification of miR-20a-5p as an oncomiR and its specific mechanism involving KLF9 provides a concrete example of a potential target for inhibition. While this study focuses on the miRNA's function and its target, it lays the groundwork for considering strategies to inhibit miR-20a-5p activity, which could theoretically involve small molecules interfering with its biogenesis, stability, or interaction with KLF9 mRNA.

On the other hand, several miRNAs are identified as tumor suppressors in NSCLC, often found at reduced levels. For example, miR-153-3p is reported to be lowly expressed in gefitinib-resistant NSCLC compared to sensitive tumors.[18] Its

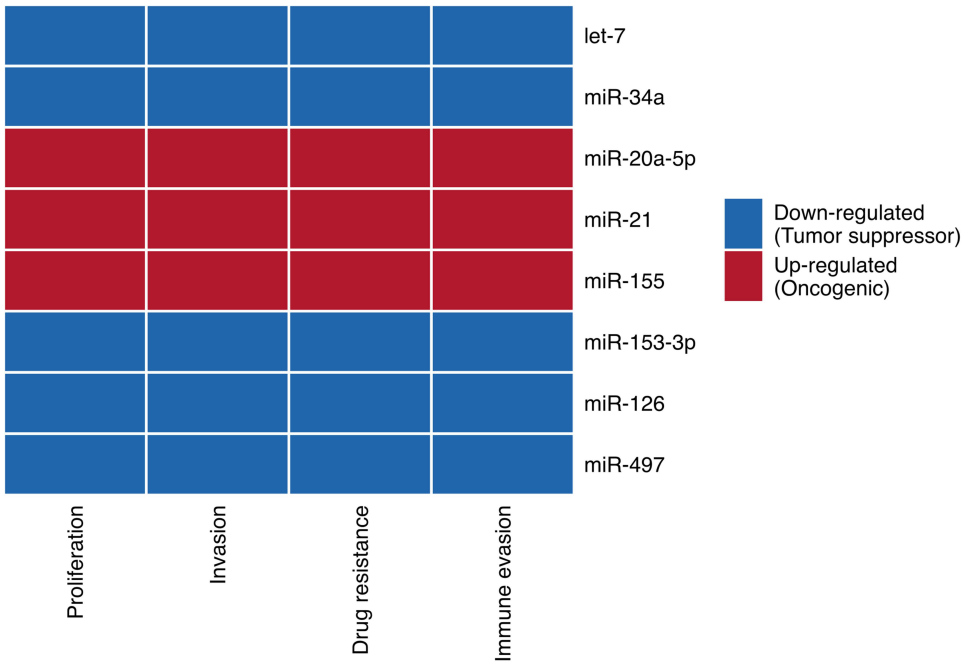


**Figure 2** Functional Heatmap of Dysregulated miRNAs in NSCLC.


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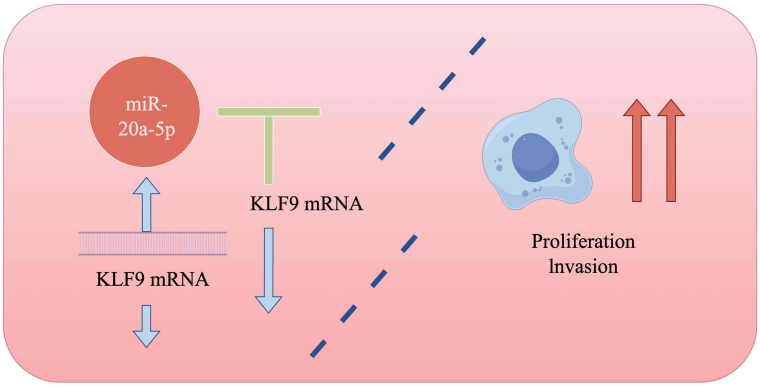


**Figure 3** Schematic representation of the miR-20a-5p/KLF9 regulatory axis in NSCLC. miR-20a-5p is significantly upregulated and suppresses the expression of KLF9 mRNA (green T-bar), leading to its downregulation (blue downward arrows). The dashed line separates the molecular regulatory process (left) from the cellular outcomes (right). The upregulation of miR-20a-5p enhances cell proliferation and invasion (red upward arrows), whereas KLF9 acts as a tumor suppressor.

expression is negatively correlated with autophagy activity, a process often implicated in drug resistance. Overexpression of miR-153-3p significantly inhibited autophagy in resistant cells, enhancing their sensitivity to gefitinib and promoting apoptosis.[18–20] The mechanism involves direct targeting and downregulation of ATG5 (Autophagy-related 5), a crucial protein in the autophagy pathway. High ATG5 levels were found in gefitinib-resistant NSCLC and were negatively correlated with miR-153-3p expression.[19] Restoring ATG5 expression reversed the effects of miR-153-3p overexpression on autophagy, gefitinib sensitivity, and apoptosis, confirming the miR-153-3p/ATG5 axis as a regulator of drug resistance.[19] Similarly, miR-126 and let-7 family miRNAs are recognized tumor suppressors often downregulated in lung cancer.[21–25] MiR-126 has been shown to suppress NSCLC cell proliferation and migration by interrupting the PTEN/PI3K/AKT signaling pathway.[14] Recent studies have demonstrated that multiple miRNAs contribute to regulating cell growth, stemness, drug resistance, and immune evasion in NSCLC, partly through pathways such as PD-L1 and other immune checkpoint signaling mechanisms.[26] MiR-34a is another well-established tumor suppressor miRNA often lost or downregulated in lung cancer, with therapeutic potential.[25,27] MiR-497 has also been identified as a tumor suppressor, inhibiting tumor growth and angiogenesis by targeting genes like YAP1, HDGF, CCNE1, and VEGF-A.[13] While these studies focus on the therapeutic potential of restoring these tumor suppressor miRNAs (using mimics), their identification and the elucidation of their mechanisms and target pathways (KLF9, ATG5, PTEN/PI3K/AKT, PD-L1, YAP1, VEGF-A, etc.) are crucial for understanding the broader landscape of miRNA-mediated regulation in NSCLC. This knowledge is indirectly relevant to targeting oncogenic miRNAs, as it highlights the critical pathways controlled by miRNAs that could be modulated by inhibiting oncomiRs.

## miRNAs in NSCLC Drug Resistance and Immune Evasion

Acquired resistance to targeted therapies, particularly EGFR-TKIs like gefitinib and erlotinib, is a major clinical challenge in NSCLC (Ahmad et al, 2013; Sin et al, 2016). Gefitinib resistance was mediated by miRNA-regulated efflux pumps and survival pathways (Figure 4). MiRNAs play significant roles in mediating this resistance and immune evasion, operating through distinct molecular circuits.

As discussed, low expression of tumor suppressor miRNAs like miR-153-3p is associated with gefitinib resistance, and restoring its levels can re-sensitize cells by inhibiting autophagy via ATG5 downregulation.[19] This suggests that therapeutic strategies aimed at modulating miRNA levels or activity could be employed to overcome drug resistance. The research specifically discusses the implications of miRNAs in gefitinib-resistant NSCLC, highlighting how manipulating endogenous miRNA levels, particularly through the use of miRNA mimetics, can attenuate signaling pathways like EGFR/PI3K/Akt and restore apoptotic cell death in resistant models.[4] While this review focuses on miRNA mimetics for tumor suppressors, it underscores the principle that targeting miRNA pathways can impact drug sensitivity.

To further illustrate the complex interplay between signaling pathways, miRNAs, and drug resistance, research has implicated the Hedgehog (Hh) signaling pathway in epithelial-to-mesenchymal transition (EMT) and subsequent

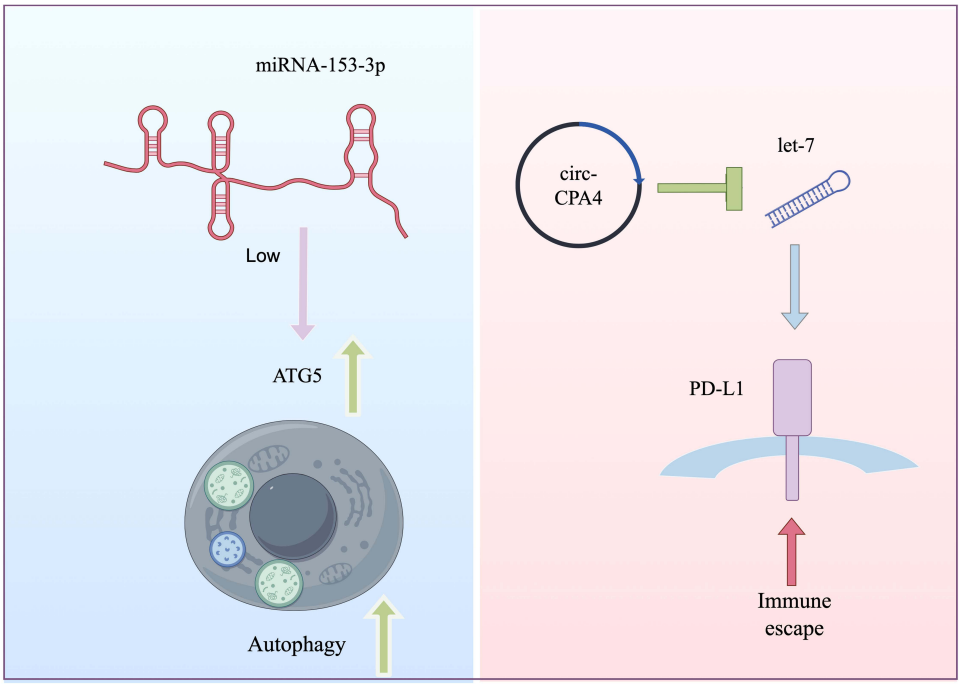


**Figure 4** Dual miRNA-Driven Mechanisms of Gefitinib Resistance and Immune Escape in NSCLC.

resistance to EGFR-TKIs and cisplatin in NSCLC.[5] Inhibition of Hh signaling, using either siRNA or the small molecule antagonist GDC-0449, was shown to abrogate resistance and re-sensitize NSCLC cells to erlotinib and cisplatin.[28] Importantly, this effect was associated with changes in the expression of EMT-regulating miRNAs. Specifically, Hh inhibition led to the attenuation of cancer stem cell markers and, critically, the upregulation of tumor suppressor miRNAs like miR-200b and let-7c, which are typically downregulated in mesenchymal/resistant cells. Ectopic overexpression of miR-200b and let-7c mimics significantly diminished erlotinib resistance, confirming their role in mediating sensitivity.

This study is particularly noteworthy because it involves a small molecule (GDC-0449); however, it targets a signaling pathway (Hh) that indirectly modulates miRNA expression, rather than directly targeting the miRNA itself or its function.[29] This highlights an alternative strategy where small molecules targeting upstream regulators can influence the miRNA landscape and impact therapeutic response, distinct from directly inhibiting an oncogenic miRNA.

Beyond drug resistance, miRNAs are also involved in shaping the tumor immune microenvironment and facilitating immune evasion. Recent evidence suggests that miRNAs play critical roles in tumor immune evasion in NSCLC, in part by modulating PD-L1 expression and other immune checkpoint pathways.[26,30] High PD-L1 expression promotes cancer progression, drug resistance, and facilitates tumor immune evasion by inactivating CD8+ T cells. Knockdown of circ-CPA4 increases let-7 levels, leading to downregulation of PD-L1 and inhibition of cell growth, mobility, stemness, and drug resistance, while also re-activating CD8+ T cells in co-culture systems.[31] This study illustrates how complex non-coding RNA networks involving miRNAs can regulate immune checkpoints, suggesting that modulating these networks could enhance immunotherapy. While this study focuses on circRNA/miRNA interaction and its downstream effects, it identifies let-7 as a critical miRNA involved in immune evasion, making its regulatory axis a potential target. Again, this study does not explore small molecule inhibitors targeting the miRNA or the circRNA directly, but highlights a mechanism relevant to the broader goal of modulating miRNA function for therapeutic benefit. The combination of miRNA-based therapy (specifically miR-34a delivery) with immunotherapy (Jurkat T cells) further explores the interaction between miRNAs and the immune system, demonstrating synergistic effects on cancer cell death.[32] This study used iron oxide nanorods (IONRs) for miR-34a delivery, showcasing a delivery strategy for RNA therapeutics and highlighting the potential for combining miRNA modulation with other treatment modalities like immunotherapy.


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## Rationale for Targeting miRNAs with Small Molecules in NSCLC

A major hurdle in translating miRNA-based therapies to the clinic is the effective and safe delivery of these charged, relatively unstable RNA molecules to tumor cells in vivo.[9,33] The following figure illustrates the representative platform and technical characteristics of miRNA delivery vectors in NSCLC treatment (Figure 5).

The provided literature highlights several innovative approaches being explored to address this challenge, primarily focusing on delivering tumor suppressor miRNA mimics. The research demonstrated the systemic delivery of synthetic miRNA mimics (miR-34a and let-7) using a novel neutral lipid emulsion in mouse models of lung cancer.[12] This approach resulted in preferential targeting of the mimics to lung tumors and led to a significant decrease in tumor burden, providing direct evidence for the feasibility of systemic delivery of miRNA mimics for lung cancer therapy.[34] This study was a pioneering effort showing in vivo efficacy of miRNA replacement therapy delivered systemically.

Exosomes, naturally occurring nanovesicles involved in intercellular communication, have emerged as promising carriers for delivering therapeutic molecules, including miRNAs, due to their biocompatibility, low immunogenicity, and ability to protect cargo from degradation.[13,14] The research demonstrated that exosomes derived from breast cancer cells (MDA-MB-231) could be engineered for lung-specific delivery to NSCLC cells (A549) via interaction between exosomal integrin β4 and surfactant protein C (SPC) on cancer cells.[14] Loading these exosomes with miR-126 mimics resulted in effective suppression of A549 cell proliferation and migration in vitro and significant inhibition of lung metastasis in vivo after intravenous administration, showcasing the potential of leveraging exosome organotropism for targeted delivery. Similarly, they utilized human cell-derived exosomes to deliver miR-497 mimics to NSCLC cells. They demonstrated that exosome-mediated delivery of miR-497 effectively suppressed tumor growth and angiogenesis-related gene expression in 2D and 3D microfluidic models, highlighting the utility of exosomes as carriers and the value of advanced in vitro models for testing these therapies.[13,35] The combination of miR-34a delivery using iron oxide nanorods (IONRs) with immunotherapy further illustrates the exploration of different delivery vehicles for miRNA therapeutics, demonstrating enhanced cancer cell killing in combination with activated T cells.[36,37]

These studies collectively demonstrate significant progress in developing delivery systems for RNA-based miRNA therapeutics (mimics or inhibitors). However, they do not address the delivery challenges specific to small molecule inhibitors targeting miRNAs. Small molecules generally have different pharmacokinetic and pharmacodynamic properties compared to nucleic acids, and their delivery might require different strategies, although some small molecules can readily enter cells. The success in delivering RNA therapeutics highlights the broader effort to translate miRNA-based interventions, providing valuable lessons regarding targeting tumor tissue and minimizing systemic toxicity, which could potentially inform the development and delivery of small molecule miRNA inhibitors.

## Mechanisms of Small Molecule Inhibition of Oncogenic miRNAs

Despite the extensive literature on the roles of miRNAs in NSCLC and the exploration of RNA-based therapeutic strategies (miRNA mimics, anti-miRs, delivery systems), the provided references contain remarkably little information specifically on small molecule inhibitors designed to directly target oncogenic miRNAs. As noted, the study involves a small molecule (GDC-0449), but it targets the Hedgehog signaling pathway, which indirectly affects miRNA levels.

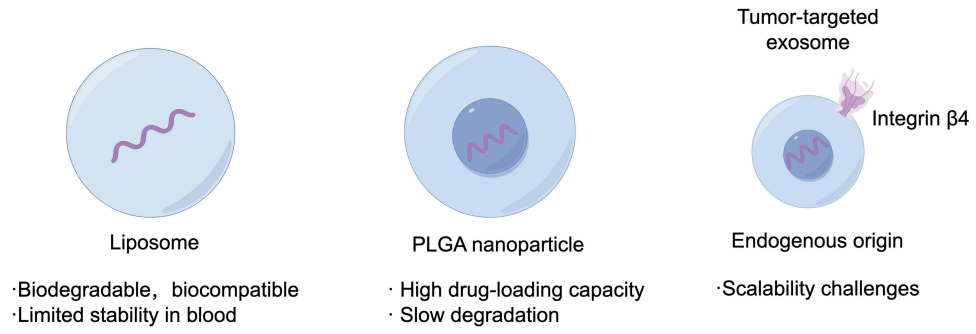


**Figure 5** Representative delivery vehicles for miRNA-based therapeutics.

This is distinct from a small molecule that, for example, binds to a specific oncogenic miRNA to block its interaction with target mRNAs, interferes with its processing by Dicer or Drosha, or promotes its degradation.[38,39]

Studies specifically detailing small molecule inhibitors directly targeting miRNAs among the provided literature suggest that this particular research direction, while conceptually promising as outlined in the abstract, may still be in its very early stages, or perhaps less represented in this specific set of retrieved papers compared to RNA-based approaches and the study of miRNA function.[13] Developing small molecules that can specifically and potently bind to or interfere with the function of a particular miRNA, which are small, single-stranded RNA molecules lacking complex protein structures, presents unique chemical and biological challenges. Unlike protein targets with well-defined binding pockets, RNA structures are often more dynamic and less amenable to traditional small molecule drug design approaches. Figure 6 summarizes the three types of action pathways for small molecule inhibition of cancer-related miRNAs. In addition to the mechanistic diversity of small molecule inhibitors, their pharmacokinetic and delivery profiles provide distinct advantages over oligonucleotide-based therapies. Small molecules typically exhibit greater chemical stability, improved tissue penetration, and can often be administered orally, unlike oligonucleotide-based agents that usually require complex delivery systems. These favorable properties enable broader systemic exposure and potentially reduce the need for specialized carriers such as lipid nanoparticles or exosomes. Furthermore, small molecules benefit from established drug development pipelines, facilitating optimization for bioavailability, metabolic stability, and safety profiles. However, their off-target effects and the challenge of achieving high specificity toward RNA targets remain key limitations that require further research and rational design strategies.

## Non-Coding RNA Networks and miRNA Regulation

The regulatory landscape within cells is highly interconnected, with miRNAs participating in complex networks involving other ncRNAs, particularly long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). A prominent mechanism is the competing endogenous RNA (ceRNA) hypothesis, where lncRNAs and circRNAs act as molecular sponges, binding to shared miRNAs and thereby regulating the expression of miRNA target mRNAs.[40,41] This adds another layer of complexity to the function of miRNA and provides additional potential intervention points.[42] The study provides a comprehensive review of the various mechanisms by which lncRNAs regulate gene expression in NSCLC,

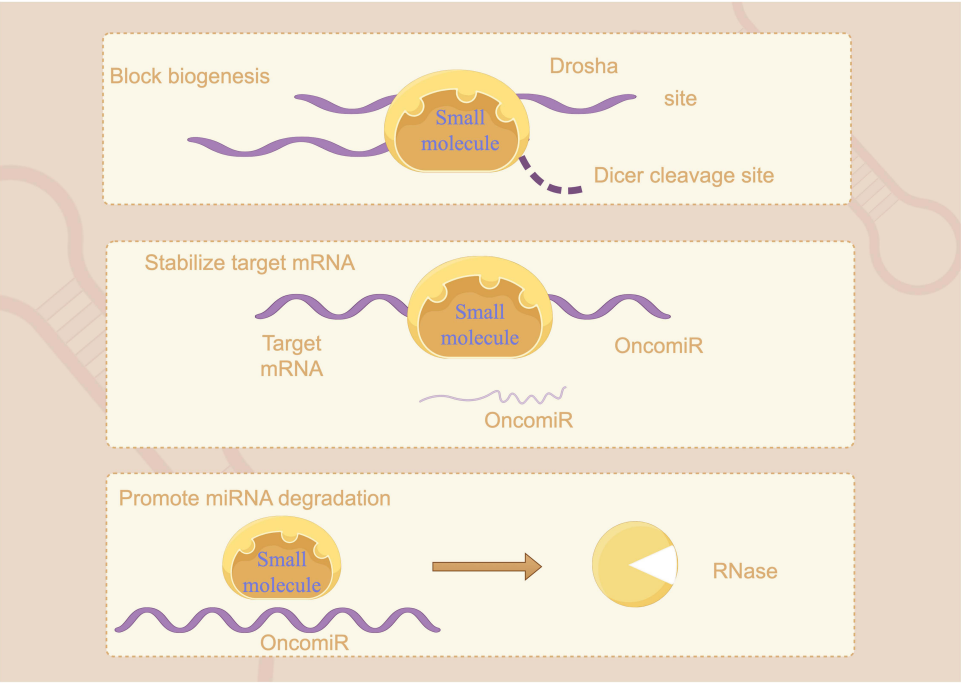


**Figure 6** Three Mechanistic Avenues for Small-Molecule Inhibition of Oncogenic miRNAs.


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highlighting that the competitive binding of lncRNAs and mRNA to miRNAs is one of the most common mechanisms. They discuss how specific lncRNAs can regulate target genes through this lncRNA/miRNA/mRNA interactome, influencing crucial pathways like JAK-STAT, Hippo, cytokine pathways, VEGFA-VEGFR2, cell cycle regulation, and neovascularization.[41,43] Examples of lncRNAs involved in multiple mechanisms, including miRNA sponging and interaction with RNA-binding proteins (RBPs), are provided.[41,44] While this review focuses on lncRNAs and their interaction with miRNAs and RBPs, it underscores the fact that miRNA activity is not isolated but is part of a larger regulatory network. Modulating the expression or activity of lncRNAs or RBPs could indirectly impact miRNA function, offering alternative strategies that might involve small molecules targeting these associated factors, although this is not explicitly discussed in the provided literature in the context of small molecule inhibitors targeting miRNAs. Understanding these networks is crucial for predicting the effects of targeting specific miRNAs and for identifying potential off-target effects or compensatory mechanisms.

## Case Studies and Preclinical Data of miRNA-Targeting SMs in NSCLC

In NSCLC, preclinical studies have explored the use of synthetic miRNA mimics, such as MRX34, or systems like viral vectors and nanoparticles to restore the function of tumor-suppressing miRNAs that are downregulated. For example, miR-34a supplementation has been shown to effectively inhibit tumor cell proliferation, promote apoptosis, and hinder migration.[45,46] MRX34, delivered by nanoparticles, showed good targeting and efficacy in lung cancer models, which could not only inhibit tumor growth and induce apoptosis but also enhance the sensitivity of chemotherapeutic drugs.[46] Although it has not been widely applied in clinical practice, these results laid an important foundation for lung cancer treatment based on miRNA replacement therapy.

On the other hand, for oncogenic miRNAs overexpressed in NSCLC (such as miR-21 and miR-155), researchers have developed specific inhibitors for targeted intervention, including antagomir (antagonist), antisense oligonucleotides (ASO) or small molecule inhibitors.[47,48] Inhibiting the activity of these miRNAs has been proven to be an effective strategy for slowing tumor proliferation and invasion. For example, using antagomir-21 to inhibit miR-21 has shown significant anti-tumor effects in various preclinical models of cancer, including lung cancer. In colon cancer models, AntimiR-21 effectively inhibited tumor proliferation and metastasis.[49] This type of miRNA inhibition therapy is currently in the preliminary clinical trial stage and shows broad application prospects in the treatment of cancers such as NSCLC. The 15-year evolution of miRNA therapeutics in NSCLC was mapped (Figure 7).

## Challenges and Future Perspectives

It is acknowledged that research into small molecule inhibitors targeting miRNAs is still in its early stages and requires sustained effort, along with the development of new technologies and chemical entities. This aligns with the limited representation of this specific topic in the provided literature. The existing studies, however, provide crucial foundational knowledge: they identify specific oncogenic miRNAs (eg, miR-20a) and their mechanisms,[50] highlight their roles in critical processes like proliferation, invasion, drug resistance, and immune evasion,[9,19,51] and map the complex non-

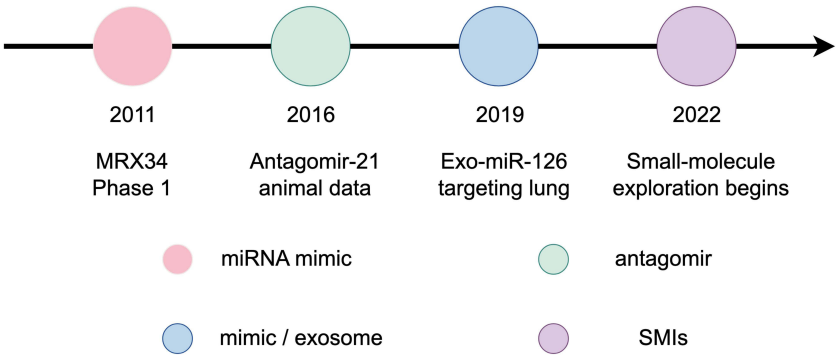


**Figure 7** Development Timeline of miRNA-Based Therapeutic Strategies in NSCLC (2011–2025).

coding RNA networks they operate within.[52,53] This information is indispensable for guiding the development of any therapeutic strategy targeting miRNAs, including future small molecule approaches. Identifying the most critical oncogenic miRNAs and understanding their precise roles and interactions are prerequisites for designing molecules that can effectively inhibit their function without causing unacceptable off-target effects.

Translational opportunities for small molecule inhibitors targeting oncogenic miRNAs, should they be successfully developed, would be significant. Compared to oligonucleotide-based therapies, small molecules often offer advantages in terms of synthesis, stability, oral bioavailability, and potentially easier delivery to various tissues. A successful small molecule inhibitor targeting a key oncogenic miRNA in NSCLC could potentially offer a new therapeutic option, either as a monotherapy or in combination with existing treatments like targeted therapies, chemotherapy, or immunotherapy, potentially overcoming resistance mechanisms or enhancing anti-tumor immune responses. The studies on miRNA mimics overcoming drug resistance and enhancing immunotherapy suggest that modulating miRNA activity has therapeutic potential; a small molecule approach could be an alternative way to achieve similar beneficial outcomes by inhibiting oncogenic miRNAs.[19,54–56]

## Concluding Remarks

In conclusion, while the provided literature extensively details the critical roles of miRNAs in NSCLC pathogenesis, drug resistance, and immune evasion, and explores various RNA-based therapeutic delivery strategies, it offers limited direct insight into the development or application of small molecule inhibitors specifically designed to target oncogenic miRNAs. The studies highlight key oncogenic miRNAs and their mechanisms, which are essential for target identification. They also demonstrate the therapeutic potential of modulating miRNA activity using alternative methods (miRNA mimics, pathway inhibitors affecting miRNAs). The field of small molecule inhibitors directly targeting miRNAs appears, based on this literature set, to be in its infancy, requiring substantial future research to identify suitable chemical scaffolds, understand the structural biology of miRNA-small molecule interactions, and develop effective and specific inhibitors for clinical translation in NSCLC. Among the oncogenic miRNAs that have been most consistently reported across NSCLC studies, miR-21, miR-155, and miR-221/222 may represent the most promising candidates for future small-molecule-based therapeutic development, given their well-established regulatory roles in tumor growth, metastasis, and drug resistance. Continued research efforts, coupled with advancements in chemical biology and drug discovery technologies, are crucial to realize the potential of this innovative therapeutic paradigm for reshaping NSCLC treatment.

## Data Sharing Statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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All schematic figures were generated using FigDraw (www.figdraw.com).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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