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THERAPEUTIC ROLE OF siRNA IN GASTRIC CANCER: GENE SILENCING MECHANISMS AND NANOCARRIER-BASED DELIVERY STRATEGIES

Gastric cancer (GC) continues to be a significant global contributor to cancer-related mortality, primarily due to late-stage diagnoses, tumor heterogeneity, and the frequent emergence of therapeutic resistance. Despite advancements in surgical techniques, chemotherapy, targeted therapies, and immunotherapy, long-term survival rates remain unsatisfactory, underscoring the need for innovative, molecularly driven approaches. SiRNA has emerged as a promising gene-silencing tool capable of selectively downregulating oncogenic drivers and pathways associated with resistance via RNA interference. Preclinical studies using GC models demonstrate promising biological activity following siRNA-mediated suppression of various molecular targets — including CD44v6, Rac1, and ZNRD1—leading to reduced cell proliferation, inhibited migration and invasion, enhanced apoptosis, and increased chemosensitivity. However, the successful translation of siRNA-based strategies into clinical practice is fundamentally reliant on the development of efficient and safe delivery systems. Recent advancements in nanotechnology have enabled the development of multifunctional nanocarriers, including lipid-based nanoparticles, peptide-based systems, chitosan-derived platforms, exosome-mimetic vesicles, layer-by-layer architectures, and stimuli-responsive theranostic nanoparticles. These engineered platforms are designed to enhance siRNA stability, improve tumor targeting, facilitate intracellular trafficking, and promote endosomal escape while minimizing off-target effects and immune activation. Preclinical findings suggest significant biological potential; however, additional research is required to address issues concerning biodistribution, safety, scalability, and regulatory standardization before clinical application. Overall, siRNA-based strategies may play a crucial role in the future development of precision-oriented therapeutic frameworks in GC research. Importantly, this review emphasizes the integration of molecular target selection with delivery system design in a GC-specific context. By systematically linking validated siRNA targets with corresponding nanocarrier strategies, this work provides a more application-oriented and translationally relevant perspective that is not typically addressed in conventional RNA interference or nanocarrier-focused reviews.

Keywords: siRNA, gastric cancer, gene silencing, nanocarrier delivery, RNA interference.

Gastric cancer (GC) remains a major global health burden and continues to be associated with unfavorable clinical outcomes, particularly in advanced or metastatic stages. Despite substantial progress in molecular profiling and therapeutic stratification, long-term survival rates remain limited for a sig-

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nificant proportion of patients. Tumor heterogeneity, dynamic alterations in the tumor microenvironment, and the frequent emergence of intrinsic and acquired therapeutic resistance collectively compromise the efficacy of conventional treatment modalities [1—3]. Present management strategies predominantly rely on surgical resection for localized disease and on systemic therapies, including chemotherapy, targeted agents, and immunotherapy, for advanced cases. However, the development of resistance and the limited durability of the response remain persistent challenges in clinical practice [2, 4]. These limitations have stimulated growing interest in molecularly guided strategies that selectively modulate resistance-associated and oncogenic signaling pathways. Among emerging approaches, RNA interference (RNAi), particularly small interfering RNA (siRNA), has attracted considerable attention as a sequence-specific gene-silencing technology. In experimental models of GC, siRNA-based interventions have been investigated for targeting oncogenic drivers, metastasis-related regulators, and multidrug resistance–associated genes [4, 5]. By enabling precise transcript suppression, siRNA offers a framework for pathway-directed modulation rather than nonspecific cytotoxic intervention. Nevertheless, the therapeutic applicability of siRNA is critically dependent on the development of efficient and biocompatible delivery systems. The naked siRNA molecules are inherently unstable in systemic circulation and exhibit limited cellular internalization, necessitating protective and targeted nanocarrier platforms to achieve functional gene silencing [5]. Consequently, advances in nanotechnology — including lipid-based nanoparticles, polymeric systems, peptide-assisted vectors, biomimetic vesicles, and stimuli-responsive architectures — have become central to the translational advancement of siRNA-based strategies in oncology. GC is a multifactorial disease driven by infectious, environmental, genetic, and lifestyle-related determinants. *Helicobacter pylori* infection is still the most well-known cause of chronic inflammation and molecular changes that lead to cancer. The diverse molecular landscape of GC highlights the participation of various signaling networks, thereby supporting the justification for gene-targeted regulatory strategies, such as siRNA-based modulation [6, 7]. In this context, the present review provides a comprehensive and translationally oriented overview of siRNA-based gene-silencing strategies in GC. Particular emphasis is placed on the molecular targets implicated in tumor progression and drug resistance, comparative evaluation of emerging nanodelivery platforms, and the key biological and technological challenges that must be addressed to facilitate future clinical translation. To contextualize the clinical limitations that drive the search for molecularly targeted approaches, it is important to consider the current therapeutic landscape of GC. Although multimodal treatment strategies including surgery, chemotherapy, targeted therapy, and immunotherapy have improved disease management in selected patient populations, their overall impact remains constrained by resistance development, systemic toxi-

Table 1. **Overview of current standard therapeutic strategies for GC and their major limitations**

Treatment modality	Representative approaches	Major limitations
Surgery	Partial or total gastrectomy	Limited efficacy in advanced or metastatic disease
Chemotherapy	Fluoropyrimidine- and platinum-based regimens	Drug resistance and systemic toxicity
Chemoradiotherapy	Combined chemotherapy and radiotherapy	Benefit dependent on patient selection; treatment-related toxicity
Targeted therapy	Anti-HER2 therapy (e.g., trastuzumab)	Restricted to biomarker-positive patients; acquired resistance
Anti-angiogenic therapy	VEGFR2 inhibition (e.g., ramucirumab)	Modest survival benefit; resistance development
Immunotherapy	PD-1/PD-L1 inhibitors	Limited response rates; lack of robust predictive biomarkers

city, and limited durability of response. A structured overview of these standard treatment modalities and their major limitations is presented in Table 1 [8—13]. Several recent reviews have summarized advances in RNAi-based strategies for GC, with particular emphasis on drug resistance mechanisms and nanoscale delivery platforms [4, 5]. Several recent reviews have addressed RNAi–based strategies in GC, often focusing either on general RNAi mechanisms or on the development of nanocarrier systems as independent topics. While these studies provide valuable insights, they typically do not establish a direct relationship between the specific molecular targets and the selection of appropriate delivery platforms within a disease-specific context. In contrast, the present review adopts a structured, target-oriented approach that integrates validated siRNA targets in GC with a comparative evaluation of nanocarrier systems. By linking molecular function to delivery strategy, this work aims to provide a more translationally relevant perspective, highlighting how target selection and delivery design can be considered together rather than as separate components. This integrated framework may facilitate a more rational design of siRNA-based strategies in GC research.

This narrative review was based on a comprehensive evaluation of the available literature on siRNA-based strategies in GC. The relevant articles published between 2006 and 2025 were identified through searches in major biomedical databases and academic search engines, including PubMed and Google Scholar, using combinations of keywords such as siRNA, RNA interference, GC, and nanocarrier delivery. Both original experimental studies (in vitro and in vivo) and review articles focusing on siRNA targets, delivery systems, and therapeutic effects in GC were included. Studies not directly related to GC or siRNA-based approaches were excluded. The selected literature was analyzed qualitatively, with particular emphasis on underlying biological mechanisms, delivery strategies, and their potential translational relevance.

RNAi

RNAi is a post-transcriptional gene regulation mechanism that enables cells to control gene expression through small RNA molecules. RNAi-related processes play a fundamental role in maintaining cellular homeostasis and regulating biological responses under physiological and pathological conditions. In cancer, dysregulation of RNAi-associated pathways has been linked to abnormal gene expression, tumor progression, and altered responses to therapy. In GC, accumulating evidence indicates that RNAi-related regulatory mechanisms contribute to disease development and therapeutic resistance. These observations have established RNAi as a relevant biological framework for gene-silencing approaches and have provided the rationale for exploring RNAi-based strategies as emerging therapeutic tools in GC [14, 15]. Among the various approaches related to RNAi, siRNA has emerged as the most thoroughly studied modality, known for its high sequence specificity and predictable gene-silencing activity. In contrast to broader RNAi mechanisms, siRNA enables direct and targeted suppression of predefined transcripts, allowing precise modulation of disease-associated genes. These characteristics have positioned siRNA as a preferred RNAi-based strategy in cancer research and therapeutic development, including GC.

SiRNAs and their general mechanism are gene regulators and belong to small RNAs, meaning they are noncoding, double-stranded RNAs (dsRNAs). Their complementary nature with mRNA allows them to silence genes. They have many biological functions, such as being involved in transcription and translation. The specific role of siRNAs in regulating proteins provides them with potential advantages over many therapies in treating incurable diseases, particularly cancers. However, while siRNA medicines are still being developed with chemical modifications, they lack an efficient delivery system, limiting their curative potential [16]. The viral RNA replication intermediates and retrotransposon transcripts are exogenous sources that comprise the long dsRNAs from which short siRNAs are derived [17]. When dsRNA enters the cytoplasm, Dicer cleaves it into siRNAs. In humans, Dicer, along with TRBP and Argonaute (Ago), forms the core of the RNA-induced silencing complex (RISC) assembly pathway. TRBP stabilizes the Dicer:dsRNA complex and facilitates the accurate processing of siRNAs. The siRNA duplex is loaded onto Ago through the RISC-loading complex (RLC), where the passenger strand is removed, and the guide strand directs target RNA silencing. This pathway is essential for

gene regulation and antiviral defense [18]. Additional proteins, such as PACT and MOV10, enhance the gene-silencing function of RISC. Although other proteins may associate with Ago complexes, they are not essential for loading RISC. Once the RLC is formed, it loads the siRNA duplex into Ago2, allowing RISC to target mRNA through various interaction modes. By receiving the siRNA duplex and positioning its 5′ ends in the phosphate-binding pocket, AGO2 cleaves the passenger strand, leading to the maturation of active RISC [19]. The incorporation of ds siRNA, synthesized by the Dicer enzyme complex (D2/R2), into the RISC initiates its interaction with Argonaute2 (Ago2). Within the RISC assembly, siRNA undergoes selective strand dissociation, where the "passenger strand" is cleaved and subsequently discarded. This precise cleavage, facilitated by the endonucleolytic activity of Ago2, ensures retention of only the "guide strand." The retained guide strand, now tightly associated with Ago2, enables the complex to recognize target mRNA. Guided by this strand, RISC is directed to complementary mRNA sequences, where Ago2 catalyzes the cleavage of target mRNA, resulting in gene silencing through the inhibition of protein synthesis [20].

Key barriers to in vivo siRNA

The therapeutic potential of RNAi has attracted significant attention, particularly in the context of cancer therapy. SiRNA, a central component of RNAi, can downregulate gene expression by promoting the degradation of target mRNA transcripts. This mechanism allows for the selective silencing of oncogenes and other disease-associated genes. However, numerous barriers related to in vivo delivery hinder the clinical translation of siRNA-based therapies, despite their specificity and versatility [21]. Among the primary challenges is the instability of siRNA under physiological conditions. In systemic circulation, siRNA molecules are rapidly degraded by serum nucleases, leading to insufficient bioavailability. Additionally, their large molecular weight and negatively charged phosphate backbone inhibit passive diffusion through the hydrophobic lipid bilayer of cell membranes, resulting in poor cellular uptake [22]. These features necessitate the use of specialized delivery systems capable of protecting siRNA and facilitating efficient internalization into the target cells. Furthermore, siRNA delivery is often complicated by off-target effects, where unintended genes may be silenced, leading to unpredictable biological responses. Another significant concern is immunogenicity, as dsRNA structures can stimulate innate immune responses, potentially triggering inflammation or systemic toxicity [21]. Therefore, overcoming these barriers is critical for the development of safe and effective siRNA-based therapeutics. In response to these challenges, recent efforts have focused on the design of multifunctional nanocarrier systems. One study introduced nucleic acid-based nanogels engineered to provide both protective and functional roles during siRNA transport. These nanogels were designed to shield siRNA from enzymatic degradation and immune detection ("defensive"), while simultaneously enhancing tumor penetration and endosomal escape ("offensive"). In vivo studies on such nanogels have reported improvements in siRNA stability and intracellular delivery efficiency, indicating their potential as delivery vehicles in RNAi research [23]. This approach highlights the potential of smart delivery systems in addressing multifaceted obstacles associated with in vivo siRNA therapy. As shown in the Figure, multiple siRNA delivery systems—including lipid-based, peptide-based, and biomimetic carriers—have been developed to overcome in vivo barriers and improve therapeutic outcomes in GC models.

Lipid-based nanocarriers

Lipid-based nanocarriers have been investigated as effective platforms for siRNA delivery in GC models. In one study, lipid nanoparticles (LNPs) were engineered to deliver siRNA targeting *TMPRSS4*, a gene associated with tumor progression and invasion in GC. The formulated LNPs exhibited efficient cellular uptake in the NUGC-3 GC cells and demonstrated intracellular localization following endocytosis, with subsequent release of siRNA into the cytoplasm. Gene silencing analysis confirmed a marked reduction in the TMPRSS4 protein expression, indicating the effective delivery and functional activity of the siRNA cargo [24]. In vivo evaluation using a GC xenograft mouse model showed enhanced accumulation of LNP-delivered siRNA within tumor tissue compared to the naked siRNA.

Notably, the combination of siRNA-loaded LNPs with fluorouracil resulted in a significant suppression of tumor growth compared to chemotherapy alone [24]. Similarly, another study developed AS1411-functionalized LNPs for targeted delivery of Bmi-1 siRNA in GC. These nanoparticles demonstrated efficient gene silencing, with Bmi-1 expression reduced by approximately 63% in the MGC-803 GC cells following treatment, which was associated with decreased tumor cell proliferation and increased apoptosis in vitro [25]. In vivo experiments further confirmed that these LNPs significantly inhibited tumor growth and promoted apoptosis in tumor tissues while maintaining favorable biosafety profiles [25]. Collectively, these findings highlight the capability of lipid-based nanocarriers to facilitate effective siRNA delivery and induce antitumor effects in preclinical GC models. Taken together, lipid-based nanocarriers appear to represent one of the most advanced and extensively investigated platforms for siRNA delivery in GC, particularly due to their ability to achieve efficient encapsulation, promote intracellular release, and demonstrate measurable in vivo tumor accumulation. However, despite these encouraging preclinical findings, several limitations remain. In particular, long-term biosafety, large-scale manufacturing reproducibility, and the stability of these systems under physiologically relevant conditions have not yet been fully clarified. Therefore, further studies are required to determine whether the delivery efficiency observed in experimental models can be consistently translated into clinically relevant therapeutic outcomes.

Peptide-based siRNA delivery systems

Peptide-assisted delivery has been investigated as an approach to enhance the intracellular transport of siRNA in GC cells. In this context, a low-molecular-weight protamine (LMWP), recognized as a cell-penetrating peptide, was used to modify PEG-SS-PEI-based nanoparticles for the delivery of BRD4-targeting siRNA. The incorporation of LMWP improved the cellular uptake of siRNA nanoparticles, as indicated by increased fluorescence intensity in the HGC-27 and SGC-7901 cells compared to non-modified systems. Intracellular localization studies showed that the nanoparticles were initially associated with lysosomes following uptake, while LMWP modification facilitated the escape of siRNA into the cytoplasm over time. Additionally, the nanocarrier system exhibited redox-responsive behavior, with enhanced siRNA release in glutathione-containing environments, suggesting a responsive release profile under intracellular conditions. Functional analyses demonstrated that delivery of BRD4 siRNA using LMWP-modified nanoparticles was associated with reduced proliferation, migration, and invasion of GC cells. These effects were accompanied by decreased BRD4 expression and modulation of downstream signaling pathways, including PI3K/AKT and c-MYC. Overall, these findings indicate that peptide-modified nanocarriers can improve the delivery efficiency and intracellular release of siRNA in GC cells, supporting their role in the development of siRNA delivery systems [26]. In contrast to carrier systems that primarily enhance systemic stability or tumor accumulation, peptide-assisted platforms appear to exert their main advantage at the intracellular level, particularly by facilitating membrane translocation and promoting endosomal escape. This feature is especially relevant in the context of siRNA delivery, where inefficient cytoplasmic release remains a key limiting factor. Nevertheless, despite these functional advantages, the broader applicability of peptide-based systems remains uncertain. Their susceptibility to enzymatic degradation, relatively short circulation time, and potential variability in delivery efficiency across different tumor microenvironments may limit their performance beyond controlled experimental settings. Consequently, further investigation is required to determine whether these systems can achieve consistent in vivo stability and delivery efficiency suitable for translational application.

Polymeric and polyelectrolyte-based systems

Polymeric and polyelectrolyte-based delivery systems have been widely investigated as platforms for siRNA delivery due to their structural versatility and their ability to form stable complexes through electrostatic interactions. In GC, cationic polymers such as polyethyleneimine (PEI) have been extensively employed to condense negatively charged siRNA into nanoscale complexes, facilitating cel-

lular uptake and intracellular delivery [27, 28]. The efficiency of these complexes is strongly influenced by the nitrogen-to-phosphate (N/P) ratio, which plays a critical role in determining stability, transfection efficiency, and cytotoxicity [27]. Surface modification of polymeric carriers with polyethylene glycol (PEG) has been shown to improve their performance in biological environments. PEGylated systems, such as PEG–g–PEI, exhibit enhanced stability, reduced cytotoxicity, and improved biocompatibility while maintaining efficient siRNA condensation and delivery capabilities. These modifications also contribute to better dispersion and interaction with GC cells, supporting more effective intracellular transport of siRNA [28]. In addition to nanoparticle-based systems, polymer–siRNA complexes have also been incorporated into advanced delivery platforms such as hydrogels to achieve sustained release profiles. For example, PEI-based siRNA complexes embedded in in situ-forming hydrogels have demonstrated prolonged retention and enhanced delivery efficiency in GC models while maintaining gene silencing activity over extended periods [29]. Despite these advantages, polymer-based siRNA delivery systems still face several challenges, including cytotoxicity associated with cationic polymers and the need for further optimization of delivery efficiency and specificity, particularly in terms of targeting specific tissues and minimizing off-target effects. Ongoing studies, therefore, focus on improving polymer design and developing safer and more efficient delivery platforms [27—29]. From a formulation perspective, polymeric and polyelectrolyte-based systems offer a high degree of tunability in siRNA delivery, allowing precise control over particle size, surface charge, and release kinetics. This flexibility enables the design of delivery platforms that can be adapted to specific biological requirements in GC models. However, a fundamental challenge in these systems lies in balancing transfection efficiency with biocompatibility. While higher cationic charge densities may improve siRNA condensation and cellular uptake, they are also associated with increased cytotoxicity and potential adverse interactions with biological components. Moreover, the performance of these systems can be influenced by variations in formulation parameters and biological conditions, which may affect their reproducibility and consistency. Therefore, further optimization is required to achieve a balance among delivery efficiency, safety, and scalable production for potential translational applications.

Chitosan-based nanoparticles

Chitosan-based nanoparticles have been extensively investigated as non-viral carriers for siRNA delivery due to their ability to form electrostatic complexes with negatively charged nucleic acids. In GC models, chitosan has been used to encapsulate siRNA into nanoscale particles, facilitating cellular uptake and intracellular delivery. For instance, chitosan-mediated delivery of BRAF siRNA has been shown to effectively reduce target gene expression in GC cells, demonstrating the capability of these systems to support RNAi processes [30]. Structural modification of chitosan has also been explored to improve delivery performance under gastrointestinal conditions. The modified chitosan derivatives, including imidazole-grafted and trimethylated forms, have been utilized to enhance nanoparticle stability and enable penetration through the gastric mucus barrier, allowing more efficient interaction with gastric epithelial and carcinoma cells. These systems, relying on spontaneous electrostatic interactions to form siRNA-loaded nanoparticles, have demonstrated the ability to modulate gene expression in relevant gastric cell models [31]. In addition, advanced chitosan-based nanocarriers have been developed for co-delivery applications. Cholesterol-modified chitosan micelles have been designed to simultaneously incorporate siRNA and hydrophobic drugs, forming stable nanostructures with suitable physicochemical properties, such as controlled particle size and surface charge. These systems have shown improved cellular uptake and enhanced intracellular delivery behavior in GC cell lines, supporting their use as multifunctional delivery platforms [32]. Despite these developments, chitosan-based systems still require further optimization in terms of stability, delivery efficiency, and reproducibility. Current approaches therefore focus on structural modification and formulation strategies to improve performance in biological environments [30—32]. As biocompatible and mucoadhesive polymers, chitosan-based systems are particularly relevant for GC applications, where interaction with the gastrointestinal environment plays a critical role in delivery performance. Their ability to

penetrate the gastric mucus layer and form stable electrostatic complexes with siRNA provides a context-specific advantage over some synthetic carriers. However, despite these favorable properties, variability in physicochemical characteristics—such as degree of deacetylation, molecular weight, and formulation conditions—can significantly influence delivery efficiency and reproducibility. In addition, maintaining nanoparticle stability under dynamic gastrointestinal conditions remains a challenge. Therefore, further standardization of formulation parameters and improved control over physicochemical properties are required to ensure consistent performance and facilitate potential translational development.

Exosome-based and biomimetic nanocarriers

Exosome-based nanocarriers have emerged as biologically derived delivery systems for nucleic acids, including siRNA, due to their inherent compatibility with cellular processes and their ability to mediate intercellular communication. In GC models, exosomes have been utilized as carriers to transfer siRNA into tumor cells, facilitating intracellular delivery through natural uptake mechanisms. For example, exosome-mediated delivery of c-MET siRNA has been shown to enable efficient internalization into GC cells and modulation of target gene expression, highlighting the suitability of these vesicles as gene delivery platforms [33]. Mesenchymal stem cell derived exosomes have also been explored as nanocarriers in GC systems due to their affinity for tumor microenvironments and their capacity for drug and nucleic acid loading. These exosomes can encapsulate therapeutic cargos such as siRNA and chemotherapeutic agents, and their nanoscale size allows effective interaction with GC cells. The experimental observations indicate that exosome-based formulations enhance cellular uptake and intracellular accumulation of the delivered molecules compared to free agents. Additionally, exosomes exhibit favorable biological properties, including low immunogenicity and natural membrane composition, which support their function as delivery vehicles in complex biological environments [34]. Their ability to transport molecular cargo across cellular barriers and deliver it directly into recipient cells further contributes to their application in siRNA delivery strategies. Nevertheless, challenges remain in controlling loading efficiency, standardizing exosome isolation, and ensuring reproducibility of these systems, which are critical considerations for further development [33, 34]. Biologically derived carriers such as exosomes offer a distinct conceptual advantage over synthetic nanocarriers, as they are inherently adapted for intercellular communication and molecular transport. This intrinsic compatibility may enhance delivery efficiency and reduce immune-related limitations in GC models. However, unlike engineered nanoparticle systems, exosome-based platforms are more difficult to standardize and control, particularly in terms of cargo loading efficiency, isolation methods, and batch-to-batch consistency. In addition, large-scale production and reproducible manufacturing remain significant challenges that limit their current translational applicability. Therefore, while exosome-based systems demonstrate promising biological functionality, further methodological optimization and standardization are required before they can be reliably integrated into therapeutic strategies.

Stimuli-responsive and theranostic delivery platforms

Stimuli-responsive delivery platforms have been developed to enhance the controlled release and intracellular availability of siRNA in cancer systems by exploiting specific features of the tumor microenvironment. In GC models, redox-responsive nanoparticles have been designed to release siRNA under elevated intracellular reducing conditions, thereby facilitating efficient cytoplasmic delivery and improving gene-silencing performance [26]. These systems rely on the environmentally sensitive linkages that remain stable under physiological conditions but undergo structural changes within tumor cells, enabling selective siRNA release. In addition to stimuli-responsive strategies, theranostic delivery platforms integrate both diagnostic and delivery functions within a single nanosystem. For instance, superparamagnetic iron oxide nanoparticle-based systems have been utilized as magnetic resonance imaging (MRI)-visible carriers for siRNA delivery in GC models [35]. These nanocarriers enable simultaneous tracking of nanoparticle distribution and cellular uptake while

mediating intracellular transport of siRNA. The incorporation of imaging capability provides real-time insight into biodistribution and delivery efficiency without altering the fundamental delivery function of the system. Overall, the combination of stimuli-responsive release mechanisms and theranostic functionalities represents an advanced approach in siRNA delivery design, allowing improved control over intracellular release and enabling monitoring of delivery processes in GC models [26, 35]. From a design perspective, stimuli-responsive and theranostic platforms introduce an additional level of functional sophistication by enabling environment-specific siRNA release and real-time monitoring of delivery processes. This dual capability may provide a strategic advantage in addressing key barriers such as inefficient intracellular release and unpredictable biodistribution. However, the increased structural and functional complexity of these systems may also introduce challenges related to formulation reproducibility, scalability, and comprehensive safety evaluation. In particular, it remains unclear whether the added multifunctionality consistently translates into superior therapeutic outcomes compared to simpler delivery systems. Therefore, further studies are required to determine the practical benefit–risk balance of these advanced platforms in the context of translational application.

Layer-by-layer nanocarriers for siRNA delivery

Layer-by-layer (LbL) assembled nanoparticles have been investigated as a strategy for enhancing the delivery efficiency of siRNA in GC models. In one study, LbL-based siRNA nanoparticles were developed to target glioma-associated oncogene homolog 1 (*GLI1*) in gastric cancer stem cells (CSCs). These nanoparticles were constructed using a LbL assembly approach and further functionalized with hyaluronic acid to enable CD44-mediated targeting. The developed nanoparticles demonstrated efficient cellular uptake and targeting capability in gastric CSCs. Functional analyses showed that GLI1 siRNA delivery via these LbL nanoparticles resulted in a significant reduction in the GLI1 protein expression. In addition, the system inhibited key cellular behaviors associated with malignancy, including tumor sphere formation, migration, and invasion of gastric CSCs. Furthermore, in vivo evaluation indicated that the nanoparticles accumulated in tumor tissues and suppressed tumor recurrence. Mechanistically, these effects were associated with the inhibition of the Hedgehog signaling pathway, which plays a critical role in the maintenance and progression of gastric CSCs. Overall, this study demonstrated that LbL-assembled siRNA nanoparticles can serve as an effective platform for targeted gene silencing in GC models, particularly through CD44-mediated delivery and pathway-specific inhibition [36]. As illustrated in the Figure, several nanocarrier platforms have been explored for the delivery of siRNA in cancer therapy, including lipid-based nanoparticles, polymeric nanoparticles, peptide-based carriers, exosomes, and other biomimetic nanovesicles, each designed to enhance siRNA stability, cellular uptake, and tumor-targeted delivery. Compared with other nanocarrier systems, LbL-assembled nanoparticles provide a highly modular and customizable platform, allowing precise control over surface composition, targeting ligands, and release behavior. This structural flexibility enables the integration of multiple functional layers that can be tailored to address specific biological barriers in GC models, particularly in the context of cancer stem cell targeting. However, despite these advantages, the current evidence remains largely based on platform-specific designs, and the reproducibility of multilayer assembly under scalable manufacturing conditions has not yet been fully established. Therefore, further studies are required to determine whether these systems can be reliably standardized and applied across broader GC contexts.

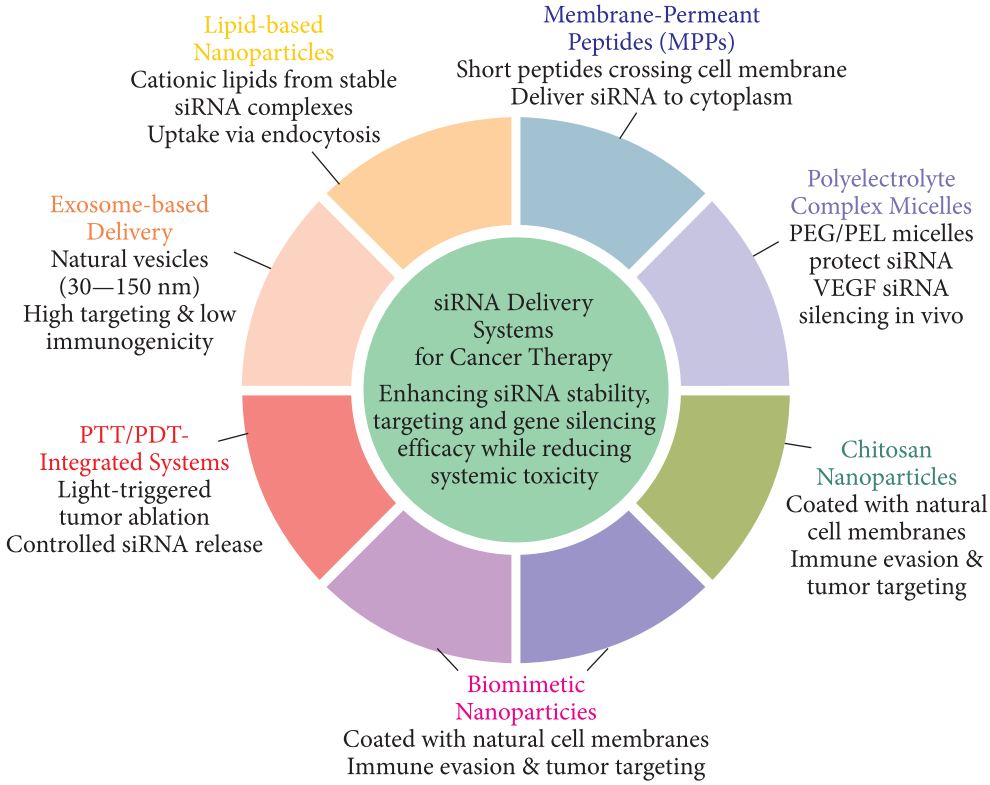
Comparison of different delivery platforms

From a broader comparative perspective, lipid-based nanoparticles appear to be among the most advanced and clinically translatable platforms due to their high encapsulation efficiency and demonstrated in vivo performance. In contrast, polymeric and chitosan-based systems offer greater structural flexibility and tunability but may be limited by cytotoxicity and formulation variability. Peptide-based carriers primarily enhance intracellular delivery and endosomal escape; however, their in vivo stability remains a concern. Exosome-derived sys-

tems provide superior biocompatibility and natural targeting capabilities, although challenges related to standardization and large-scale production restrict their translational potential. Stimuli-responsive and theranostic platforms introduce additional functional advantages, such as controlled release and imaging capability, but their increased structural complexity may affect reproducibility and clinical applicability. Overall, no single delivery system is universally optimal, and the selection of an

Table 2. **Nanocarrier-based siRNA delivery systems in GC: target genes and preclinical functional outcomes**

Delivery system	Target gene	Strategy	Experimental model	Main findings	References
Exosome mimetic nanocarriers	*NPR1*	siRNA-mediated silencing via engineered exosome mimetics	In vitro and in vivo (GC metastasis model)	*NPR1* silencing reduced lipid droplet lipolysis, decreased mitochondrial oxidative phosphorylation, and inhibited gastric cancer metastasis	[37]
Chitosan nanoparticles (CH-NP)	*RNU11*	siRNA delivery using chitosan-based nanoparticles	GCcell lines (AGS, HGC27) and xenograft mouse model	Silencing of *RNU11* inhibited GC cell proliferation, migration, and induced apoptosis	[38]
Layer-by-layer (LbL) nanoparticles	*GLI1*	siRNA delivery using LbL assembled nanoparticles	Gastric CSCs (in vitro) and in vivo tumor model	Silencing of *GLI1* reduced tumor sphere formation, migration, and invasion of gastric CSCs	[36]
PEG-SS-PEI nanoparticles (LMWP-modified)	*BRD4*	siRNA delivery using redox-responsive polymeric nanoparticles	In vitro (GC cell lines)	*BRD4* silencing inhibited proliferation, migration, and invasion via suppression of PI3K/AKT and c-MYC signaling pathways	[26]
Lipid nanoparticles (LNPs)	*TMPRSS4*	Anti-TMPRSS4 siRNA delivery using engineered lipid nanoparticles	In vitro (NUGC-3 cells) and in vivo (xenograft mouse model)	Enhanced tumor accumulation; significant tumor growth reduction; improved effect in combination with 5-FU	[24]
Folic acid–functionalized polyethyleneimine superparamagnetic iron oxide nanoparticles (FA-PEG-SS-PEI-SPION)	*PD-L1*	siRNA delivery using folic acid-functionalized PEI-based magnetic nanoparticles with disulfide linkage	GC cell line (SGC-7901)	Efficient cellular uptake and *PD-L1* gene silencing; the nanoparticles also showed MRI-related imaging potential	[35]
scFv(CD44v6)-PEG-g-PEI functionalized superparamagnetic iron oxide nanoparticles (PEG-g-PEI-SPION)	*CD44v6*	Antibody-directed siRNA delivery using PEG-g-PEI functionalized magnetic nanoparticles	In vitro and in vivo	Effective siRNA transfer, cellular uptake, and distribution confirmed by fluorescence imaging and immunofluorescence staining; targeting effect verified by MRI and histology	[39]



Schematic categorization of siRNA delivery systems relevant to GC research. The figure outlines major nanocarrier strategies distinguished by their physicochemical properties and functional mechanisms. Lipid-based nanoparticles enable efficient siRNA encapsulation and promote endosomal escape. Exosome-derived carriers offer intrinsic biocompatibility and cellular targeting capabilities. Chitosan-based systems facilitate electrostatic complexation and exhibit mucoadhesive behavior. Polyelectrolyte micelles provide tunable release kinetics and improve colloidal stability. Peptide-based vectors enhance membrane translocation and intracellular uptake. Stimuli-responsive platforms allow condition-specific release based on environmental triggers. Biomimetic nanocarriers incorporate cell-derived membranes to support immune evasion and prolonged circulation

appropriate platform should be guided by the biological characteristics of the target and the specific therapeutic context in GC. To better compare the characteristics of different nanocarrier platforms used for siRNA delivery, Table 2 summarizes representative delivery systems investigated in GC research, together with their target genes, experimental models, and reported preclinical functional outcomes.

The nanocarrier platforms summarized above highlight the critical role of delivery system design in improving siRNA stability, cellular uptake, and intracellular release in GC models. Despite these advances, most studies still operate in preclinical settings, highlighting the necessity for further validation and clinical translation. While the optimization of the nanocarrier systems is essential for efficient siRNA delivery, the observed biological effects of these approaches largely depend on the selection of biologically relevant molecular targets. In GC research, siRNA-based strategies have been widely used to investigate genes and signaling pathways involved in tumor progression and cellular processes. In this context, Table 3 summarizes the representative molecular targets and the functional outcomes observed following siRNA-mediated gene silencing in preclinical models.

Table 3 provides a structured overview of representative molecular targets examined in siRNA-based experimental studies of GC, integrating their biological roles with the phenotypic outcomes observed after gene silencing. The compiled evidence indicates that the investigated targets are primarily involved in regulatory pathways governing tumor cell proliferation, survival, apoptosis, invasion, metastasis, angiogenesis, and metabolic adaptation. Despite the heterogeneity of these targets, siRNA-mediated suppression frequently yields comparable biological effects, including reduced cell proliferation, decreased migration and invasion, and in-

creased apoptotic activity. This pattern suggests that modulation of distinct molecular pathways may yield overlapping phenotypic responses, reflecting the interconnected nature of GC signaling networks. Overall, the findings summarized in Table 3 highlight consistent functional outcomes observed in preclinical models following siRNA-mediated gene silencing. These observations should be interpreted in light of the multiple experimental and biological limitations, as further discussed in the following section.

Promising siRNA targets in GC

Among the targets summarized in Table 3, several appear particularly promising because their silencing was associated with strong antitumor effects and, in some cases, validation in both in vitro and in vivo models. PKM2, Notch1, ABL (lncRNA), STAT3, VEGF, and Survivin (BIRC5) showed high translational relevance in line with evidence from in vivo or combined in vitro/in vivo models. These targets are involved in major functional processes of GC progression, including metabolic adaptation, oncogenic signaling, apoptosis resistance, angiogenesis, drug resistance, and tumor growth. For example, siRNA-mediated knockdown of PKM2 reduced cell proliferation and tumor growth under hypoxic conditions [43], whereas Notch1 silencing enhanced doxorubicin sensitivity, induced apoptosis, and inhibited tumor growth [46]. Similarly, STAT3 silencing suppressed tumor growth, reduced proliferation, and promoted apoptosis [50], while VEGF knockdown reduced tumor volume and weight in vivo [51]. Survivin silencing also suppressed tumor growth and induced apoptosis in xenograft models [52]. Other high-value targets, including CD44v6, Bcl-X_L (BCL2L1), EZH2, and DcR3, also demonstrated biologically relevant effects following siRNA-mediated inhibition. CD44v6 is notable because of its association with CSC features, tumor progression, and metastasis, although the reported evidence primarily emphasized delivery efficiency rather than broader functional validation [27]. Bcl-X_L, EZH2, and DcR3 are mainly linked to tumor cell survival, chemoresistance, and apoptosis regulation. Their silencing enhanced cytotoxicity, inhibited proliferation, reversed cisplatin resistance, or increased sensitivity to 5-fluorouracil [44, 47, 48]. These findings suggest that apoptosis- and resistance-associated targets may be especially relevant for combination strategies in GC. In contrast, the targets with moderate translational value, including NEDD9, S100A4, ZNRD1, Rac1, ARHGAP9, and ZNF139, also produced meaningful phenotypic effects such as reduced migration, invasion, proliferation, EMT-related changes, or enhanced apoptosis [40—42, 45, 53, 54]. However, their current evidence is largely restricted to in vitro models, specific cell lines, or limited experimental contexts. Therefore, while these targets remain biologically important, further in vivo validation and more comprehensive functional assessment are required before their translational potential can be considered comparable to the high-value targets summarized in Table 3.

Challenges and future directions of siRNA therapeutics in GC

Despite the growing interest in siRNA-based strategies for GC, several critical challenges continue to limit their clinical translation. One of the primary barriers is the inherent instability of naked siRNA in biological environments, where they are highly susceptible to enzymatic degradation and rapid clearance from circulation, resulting in limited bioavailability and reduced therapeutic efficacy [5, 22]. In addition, the efficient delivery of siRNA to tumor tissues remains a major obstacle. The large molecular size and negative charge of siRNA hinder its ability to cross cellular membranes, while biological barriers such as dense extracellular matrix and abnormal tumor vasculature restrict nanoparticle penetration and distribution within gastric tumors [4, 5, 23]. In the context of GC, the additional disease-specific factors further complicate delivery efficiency. The gastric microenvironment is characterized by acidic conditions and a protective mucus layer, both of which can influence nanoparticle stability and reduce delivery performance, particularly for orally or locally administered systems [22]. Moreover, tumor heterogeneity in GC — encompassing variations in gene expression, stromal composition, and cellular subpopulations — can significantly affect target accessibility and therapeutic response [4, 23]. Even after successful cellular uptake, the intracellular barriers remain a key limitation. The endosomal entrapment reduces the cytoplasmic availability of siRNA,

Table 3. **Molecular targets in GC: functional roles, siRNA-mediated effects, and translational relevance in preclinical models**

Target	Role in GC	Evidence type	Model	Main effect of siRNA	Translational value	Limitation	Reference
NEDD9	Promotes hypoxia-induced migration via Rac1 signaling	In vitro	BGC-823, SGC-7901	siRNA-mediated knockdown reduced cell migration through modulation of the MICAL1/Rac1 pathway	Moderate	Evidence limited to in vitro models; no in vivo or clinical validation	[40]
S100A4	Promotes epithelial–mesenchymal transition (EMT) and metastasis via MYH9 regulation	In vitro	Gastric cancer cell lines	siRNA-mediated silencing reduced migration, invasion, and EMT marker expression	Moderate	Lack of in vivo validation; mechanism limited to the EMT pathway	[41]
ZNRD1	Regulates drug resistance and apoptosis via IMPDH2 and Bcl-2 pathways	In vitro	SGC7901/VCR (drug-resistant gastric cancer cells)	siRNA-mediated knockdown enhanced chemosensitivity and induced apoptosis	Moderate	Limited to a drug-resistant cell model; no in vivo validation	[42]
PKM2	Regulates cancer metabolism and proliferation under hypoxic conditions	In vitro + + in vivo	Hypoxia-resistant gastric cancer cell lines, mouse model	siRNA-mediated knockdown reduced cell proliferation and tumor growth	High	Context-specific to hypoxic conditions; limited clinical validation	[43]
CD44v6	Cancer stem cell marker associated with tumor progression and metastasis	In vitro	SGC7901 gastric cancer cells	siRNA delivered via PEG-PEI nanoparticles achieved efficient gene silencing with low cytotoxicity	High	No in vivo validation; focus on the delivery system rather than functional outcomes	[27]
Bcl-XL (BCL2L1)	Anti-apoptotic protein promoting tumor survival	In vitro	MKN-45, MKN-28 gastric cancer cells	Co-delivery of siRNA and doxorubicin via polymerosomes enhanced cytotoxicity and inhibited proliferation	High	No in vivo validation; complex delivery system	[44]
Rac1	Regulates cell migration, invasion, and cytoskeletal dynamics	In vitro	SGC803 gastric cancer cells	siRNA-mediated knockdown reduced proliferation and motility and induced apoptosis	Moderate	Limited to in vitro study; article in Chinese	[45]
Notch1	Oncogenic signaling pathway involved in proliferation and drug resistance	In vitro + + in vivo	SGC7901 gastric cancer cells; tumor model	siRNA knockdown enhanced doxorubicin sensitivity, induced apoptosis, and inhibited tumor growth	High	Limited clinical validation	[46]
EZH2	Epigenetic regulator associated with tumor progression and chemoresistance	In vitro	AGS/DDP gastric cancer cells	siRNA knockdown inhibited proliferation, induced apoptosis, and reversed cisplatin resistance	High	Includes non-gastric models; no in vivo validation	[47]

DcR3	Anti-apoptotic receptor contributing to tumor progression and immune evasion	In vitro	AGS GC cells	siRNA knockdown enhanced apoptosis and increased sensitivity to 5-fluorouracil	High	Limited to in vitro model	[48]
ABL (lncRNA)	Regulates apoptosis inhibition and multidrug resistance via APAF1 interaction	In vitro + in vivo	Xenograft and organoid GC models	siRNA-mediated silencing enhanced chemotherapy sensitivity and promoted apoptosis	High	Targets lncRNA rather than protein-coding gene	[49]
STAT3	Key oncogenic transcription factor involved in proliferation, survival, and anti-apoptotic signaling in GC	In vitro + in vivo	GC cell lines; xenograft mouse model	siRNA-mediated silencing of STAT3 inhibited tumor growth, reduced cell proliferation, and induced apoptosis	High	Limited to preclinical models; lack of clinical validation	[50]
VEGF	Promotes angiogenesis and supports gastric tumor growth	In vitro + in vivo	SGC7901 GC cells; nude mouse subcutaneous xenograft model	Lentivirus-mediated VEGF siRNA downregulated VEGF and BCL-2, upregulated p21 in SGC7901 cells, and significantly reduced tumor volume and weight in vivo	High	Preclinical only; lentiviral delivery may limit direct clinical translation	[51]
Survivin (BIRC5)	Anti-apoptotic protein involved in the inhibition of caspase activation and regulation of cell division in GC	In vivo	GC xenograft model in nude mice	siRNA-mediated knockdown of survivin suppressed tumor growth and induced apoptosis in vivo	High	Preclinical evidence only; lack of clinical validation	[52]
ARHGAP9	Regulates cell migration, invasion, and EMT in GC	In vitro	GC cell lines (e.g., SGC-7901)	siRNA-mediated knockdown inhibited proliferation, suppressed EMT, and reduced migration and invasion via inactivation of AKT/p38 signaling and downregulation of MMP2/MMP9	Moderate	Limited to in vitro data; lack of in vivo validation	[53]
ZNF139	Zinc finger protein implicated in regulation of cell survival in GC	In vitro	BGC823 GC cells	siRNA-mediated knockdown of ZNF139 reduced cell proliferation and induced apoptosis, accompanied by downregulation of BCL-2, survivin and XIAP, and upregulation of BAX and caspase-3	Moderate	Limited to in vitro data; no in vivo or clinical validation	[54]

thereby limiting gene-silencing efficiency. In addition, off-target effects and unintended immune activation remain important safety concerns, as siRNA molecules may interact with non-specific transcripts or activate innate immune pathways [5, 22]. Another major challenge is the complexity of oncogenic signaling in GC, where multiple pathways often operate simultaneously. Consequently, targeting a single gene may be insufficient to achieve sustained therapeutic effects, highlighting the need for combinational or multitarget strategies [4, 54]. Finally, most of the available evidence for siRNA-based therapies in GC is derived from preclinical studies, with limited clinical validation. The challenges related to large-scale manufacturing, formulation reproducibility, and regulatory standardization further hinder clinical translation. To address these challenges, future research should focus on the rational design of nanocarrier systems that integrate stability, targeting specificity, and efficient intracellular release. In particular, multifunctional delivery platforms capable of overcoming multiple biological barriers simultaneously may improve therapeutic outcomes [5, 23]. Combination strategies, including co-delivery of siRNA with chemotherapeutic agents, have shown potential in enhancing chemosensitivity and overcoming drug resistance in the GC models [4, 23]. In addition, advances in the chemical modification of siRNA molecules may improve stability, reduce immunogenicity, and enhance target specificity. Personalized approaches based on molecular profiling of GC may further enable the selection of optimal siRNA targets and delivery strategies [4]. Importantly, future progress will depend on the development of scalable manufacturing processes, standardized delivery systems, and well-designed clinical studies to evaluate safety and efficacy. Addressing these factors will be essential for translating siRNA-based strategies from experimental models into clinically applicable therapies for GC [5, 23].

The siRNA-based strategies represent a rapidly evolving and precision-oriented approach in GC research, particularly at the preclinical stage. Experimental studies have demonstrated that siRNA-mediated modulation of molecular targets can influence key malignant phenotypes, such as proliferation, invasion, apoptosis, and chemosensitivity. These findings underscore the potential of transcript-level intervention in addressing gastric tumor heterogeneity and resistance-associated mechanisms. Concurrently, advances in nanotechnology have enabled the development of diverse delivery platforms, including lipid-based nanoparticles, polymeric systems, chitosan-derived carriers, peptide-assisted vectors, biomimetic vesicles, and stimuli-responsive architectures. These systems are designed to enhance siRNA stability, improve tumor targeting, and facilitate intracellular release. However, despite these technological developments, significant challenges remain, particularly in vivo biodistribution, long-term safety, immune activation, manufacturing reproducibility, and regulatory standardization. Importantly, current evidence suggests that the effectiveness of siRNA-based approaches in GC is not solely dependent on target selection or delivery system design alone, but rather on the integration of both components. The coordinated consideration of molecular targets and delivery strategies may therefore represent a critical factor in improving translational outcomes. Overall, while siRNA-based modulation demonstrates considerable biological promise in GC models, further optimization of delivery systems, validation in clinically relevant settings, and standardization of translational frameworks are required before therapeutic applicability can be fully realized. The continued interdisciplinary collaboration across RNA biology, materials science, and oncology will be essential to advance the clinical potential of these strategies.

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ТЕРАПЕВТИЧНА РОЛЬ siРНК ПРИ РАКУ ШЛУНКА: МЕХАНІЗМИ САЙЛЕНСИНГУ ГЕНІВ ТА СТРАТЕГІЇ ДОСТАВКИ НА ОСНОВІ НАНОНОСІЇВ

Рак шлунка (РШ) продовжує бути значним фактором глобальної смертності від онкологічних захворювань через пізню діагностику, гетерогенність пухлин та частий розвиток лікарської резистентності. Незважаючи на досягнення в хірургічних методах, хіміотерапії, таргетній терапії та імунотерапії, довгострокові показники виживаності залишаються незадовільними, що вказує на необхідність інноваційних, молекулярно-орієнтованих підходів. Малі інтерферуючі РНК (siРНК) стали перспективними інструментами пригнічення генів, здатними вибірково пригнічувати експресію онкогенних драйверів та сигнальні шляхи, пов'язані з резистентністю, через механізми РНК-інтерференції. Доклінічні дослідження на моделях РШ демонструють ефективність пригнічення siРНК різних молекулярних мішеней, включаючи CD44v6, Rac1 та ZNRD1, що приводить до гальмування проліферації клітин, пригнічення міграції та інвазії, посилення апоптозу та підвищення чутливості до хіміопрепаратів. Однак успішне впровадження стратегій на основі siРНК в клінічну практику залежить від розробки ефективних та безпечних систем доставки. Нещодавні досягнення в нанотехнологіях сприяли створенню багатофункціональних наноносіїв, таких як наночастинки на основі ліпідів, системи на основі пептидів, платформи, отримані з хітозану, везикули, що міметують екзосоми, конструкції пошарової зборки та тераностичні наночастинки, що реагують на стимули. Ці сконструйовані платформи розроблено для підвищення стабільності siРНК, покращення таргетування пухлини, полегшення внутрішньоклітинного транспорту та сприяння виходу з ендосом, мінімізуючи при цьому вплив поза цільовою зоною та імунну активацію. Доклінічні результати свідчать про значний біологічний потенціал; однак, необхідні додаткові дослідження для вирішення питань біорозподілу, безпеки, масштабованості та регуляторної стандартизації перед клінічним застосуванням. Загалом, стратегії на основі siРНК можуть відігравати вирішальну роль у майбутньому розвитку персоналізованих терапевтичних структур у дослідженнях РШ. Цей огляд підкреслює необхідність інтегрувати вибір молекулярних мішеней з розробкою систем доставки в контексті, специфічному для РШ, що забезпечить трансляційно релевантні перспективи.

Ключові слова: siРНК, рак шлунка, пригнічення генів, доставка наноносіїв, РНК-інтерференція.