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Role of non-coding RNA through nanomedicine: the novel therapeutic and diagnostic approaches

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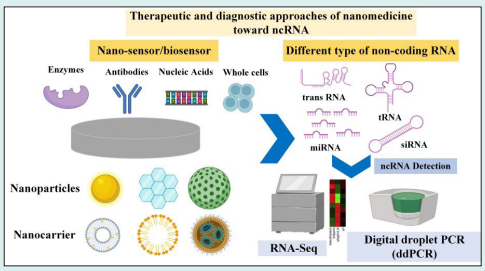
Abstract



In today's rapidly advancing field of medical research, non-coding RNA (ncRNA) and nanomedicine have emerged as promising areas of study for therapeutic and diagnostic approaches. ncRNAs, previously considered "junk DNA" and hence insignificant, are now being documented for their remarkably extraordinary regulatory roles in gene expression and various cellular processes. These molecules acquire various forms, comprising microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and small interfering RNAs (siRNAs), each with its distinct functions. The enormous benefits of ncRNA therapies include ease of sequence design and creation, functional flexibility, charge and protection, and the opportunity for patient-specific management. Nanomedicine, on the other hand, combines nanotechnology and medicine through developing innovative solutions for disease treatment and diagnosis. This article provides an overview of the technical aspects and potential of commercializing the design and targeting of ncRNAs using nanocarriers and nano-delivery systems for miRNA delivery. Furthermore, the impact of nanomedicine on the healthcare industry, as well as its therapeutic and diagnostic applications, has been investigated. Overall, this study will provide insight into novel systems for the treatment and diagnosis of ncRNA.

Introduction

Non-coding RNA

Non-coding RNA (ncRNA) refers to a class of RNA molecules that do not code for proteins.[1] Previously dismissed as "junk DNA," ncRNAs have proven to be crucial players in gene regulation, cellular development, and disease progression. These molecules come into various forms, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and small interfering RNAs (siRNAs), each with its distinct functions (Fig. 1). Long non-protein-coding RNAs > 200 nucleotides in length, some of which play crucial roles in a variety of biological processes such as promoter-specific gene regulation, epigenetic control of chromatin, X-chromosome inactivation, mRNA stability, and imprinting. Small ncRNAs are symbolized by a wide range of identified and recently discovered RNA species, with many being related to 5′ or 3′ regions of protein-coding genes. This class includes well-documented siRNAs, miRNAs, piRNAs, and others.[2,3]

Nanomedicine: Developing healthcare at the nanoscale

Nanomedicine is the application of nanotechnology in the field of medicine. It involves the design, development, and use of nanoscale materials and devices for various healthcare purposes. Nanomedicine also holds great promise for improving patient outcomes and revolutionizing healthcare. To realize the impact of nanomedicine, it is desirable to understand the nanoscale. The nanoscale refers to dimensions ranging from 1 to 100 nm, where one nanometer is equivalent to one billionth of a meter.[5] At this scale, materials exhibit unique physical,

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chemical, and biological properties that vary from their bulk complements. These properties consist of increased surface area, enhanced reactivity, and improved cellular interactions. Scientists can create innovative solutions for medical challenges by manipulating, using, and engineering materials at the nanoscale.[6]

Nanomedicine has the potential to revolutionize healthcare by enabling precise drug delivery, imaging, and diagnostics at the molecular level.

Quantitative real-time PCR (qRT-PCR), digital droplet PCR (ddPCR), RNA, and sequencing (RNA seq) are common ways to investigate ncRNA potential biomarkers.[7] By applying different materials and devices at the nanoscale, nanomedicine can offer innovative solutions for targeted treatments with reduced side effects and better-quality therapeutic outcomes.[8] For this purpose, nano-sensors/biosensors (Fig. 2), and nanoparticles (NPs) as nanocarriers are some of the main fields that play significant roles in the nanomedicine scope.[9] Multi-functionalized NPs and nano-based sensors have been developed by targeted action via binding specified ligands to target the tissues for the diagnosis and treatment of cancer.[10]

Regulatory roles of microRNAs and nanocarriers

miRNA, a type of small non-coding RNA, regulates gene expression by binding to target messenger RNAs (mRNAs) and either inhibiting their translation or promoting their degradation. They play key roles in cellular processes such as development, differentiation, and apoptosis. [2] Furthermore, dysregulation of specific miRNAs has been linked to various diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions.[3]

It is believed that among ncRNA, miRNA can be effectively applied for cancer treatment, as well as for many other purposes. For this purpose, miRNA-nanocarriers are engineered to deliver miRNA molecules to specific cellular targets with unparalleled precision. In cancer treatment, for example, these nanocarriers can

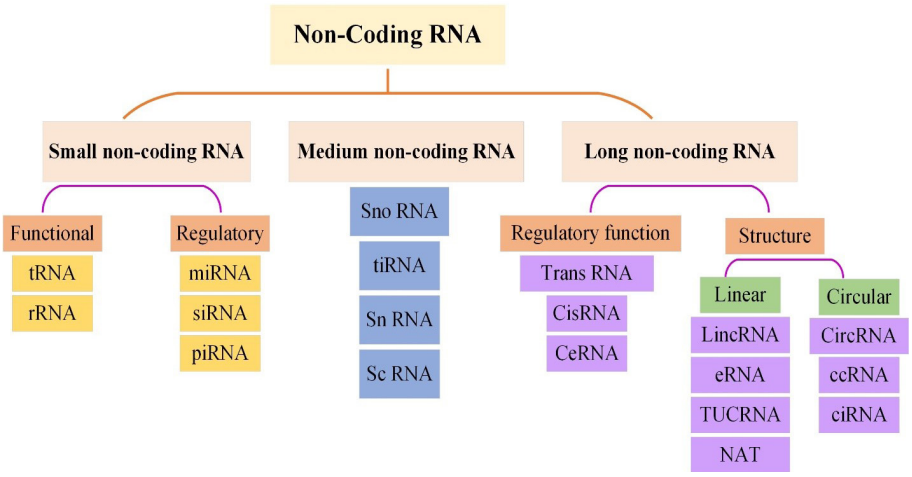

Fig. 1. The different classification of ncRNA: Function and their regulatory role

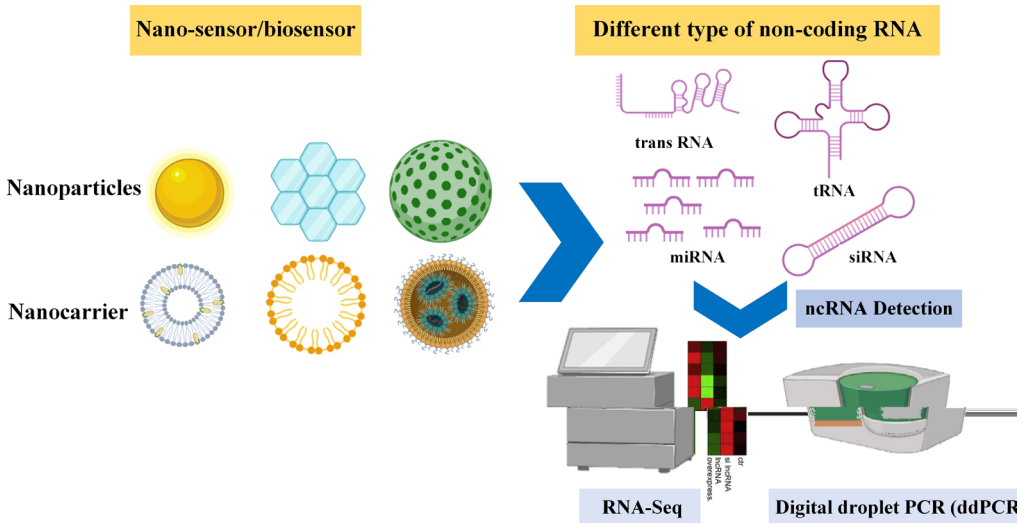

Fig. 2. Enhancement of lncRNA detection by using functionalized NPs.

deliver miRNAs that prevent tumor growth while sparing healthy tissues.

There are five major nano-delivery systems groups for miRNA delivery. (1) miRNAs can be chemically conjugated to nucleic acid/protein NPs such as antibodies, aptamers, and pRNA to support delivery. (2) Inorganic NPs are a novel delivery system with a small size of about 1-70 nm. (3) Cell-derived membrane nanocarriers can also be utilized up to 200 nm in size. (4) Lipid-based delivery systems are popular due to their high gene transfection efficiency. (5) Polymers are another efficient delivery strategy with their large size compared to other systems (up to 500 nm) (Fig. 3). It is believed that by tailoring treatment regimens based on an individual's miRNA profile, healthcare providers can improve therapy outcomes, minimize adverse effects, and enhance overall patient care.

Diagnostic and therapeutic applications of ncRNA

Although no pure ncRNA therapeutics are yet fully FDA-approved, RNA-targeting therapies are approved; none are classic "non-coding" RNAs, such as miRNAs or lncRNAs, used directly as drugs. Approved agents are primarily synthetic antisense oligonucleotides (ASOs) and siRNAs designed to target specific mRNAs. Multiple siRNA drugs are now FDA-approved, representing the most mature class of therapeutic ncRNAs. Several ASO drugs are approved, targeting non-coding regions or mechanisms involving ncRNAs.[11]

Hence, the unique characteristics and regulatory capabilities of ncRNA make them valuable targets for diagnostic and therapeutic interventions, particularly in cancer (Table 1).

Researchers have explored the use of ncRNAs as biomarkers for disease detection and prognosis.[53] ncRNA-therapies can also provide enormous benefits, including ease of sequence design and creation, functional flexibility, charge and protection, and the opportunity for patient-specific management.[54] In addition, ncRNAs can facilitate the conversion of proteins into the cellular cytoplasm without requiring nuclear entry, and are not expected to interact with the host genome, therefore verifying the safety of these treatments.[55]

By analyzing the expression profiles of specific ncRNAs, healthcare professionals can gain insights into disease states and tailor treatment strategies accordingly. Additionally, the therapeutic potential of ncRNA lies in its ability to regulate gene expression.

Small non-coding RNAs regulate gene expression post-transcriptionally, typically by binding to target mRNAs with partial complementarity, leading to mRNA cleavage or inhibition of protein synthesis. The outcome depends on the degree of complementarity between the siRNA/miRNA and its target. Perfect complementarity induces endonucleolytic cleavage of the mRNA. In contrast, imperfect pairing is more common in mammals, results

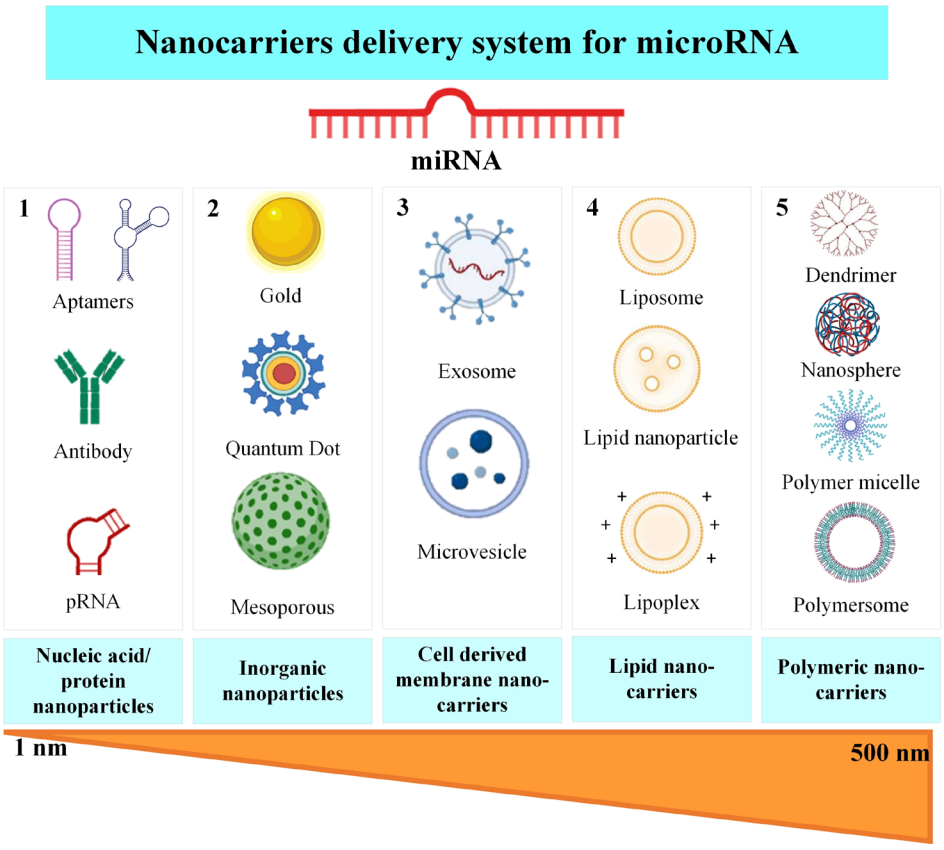

Fig. 3. Schematic illustration of nanocarriers for miRNA delivery.

Table 1. Summary of evaluating ncRNA as biomarkers for cancer

ncRNA	Associated cancer	Application	Ref.
H19 (lncRNAs)	Gastric cancer	Diagnostic, prognostic	12,13
let-7	Lung cancer	Diagnostic, prognostic	14,15
circHIPK3	Liver & colorectal cancer	Diagnostic, prognostic, therapeutic target	16,17
HOTAIR (lncRNA)	Breast & colorectal cancers	Diagnostic, prognostic, diagnose metastasis	18-23
MALAT1 (lncRNA)	Lung & breast cancers	Diagnostic, prognostic, diagnose metastasis	24,25
lncRNA GAS5	Breast & prostate cancer	Diagnostic, prognostic, therapeutic target	26,27
lncRNA PCA3	Prostate cancer	Diagnostic, prognostic	28,29
circPVT1	Gastric & colorectal cancer	Diagnostic, prognostic	18,30-32
lncRNA SChLAP1	Prostate cancer	Diagnostic, prognostic, diagnose metastasis	33, 34
piRNAs	Various cancers	Diagnostic, prognostic	35,36
miR-21	Various cancers	Diagnostic, prognostic, therapeutic target	37,38
miR-155	Breast Cancer & esophageal squamous cell carcinoma	Diagnostic, prognostic	39-42
miR-34a	Prostate, lung & breast cancers	Diagnostic, prognostic, therapeutic target	43-46
miR-125b	Breast & ovarian cancer	Diagnostic, prognostic, therapeutic target	47-52
miR-15b miR-21	Colorectal cancer	Diagnostic	NCT06738225
miR-20a	Gastric cancer	Diagnostic	NCT05901376
miR-21	Gastric cancer	Diagnostic	NCT05901376
miR-106b	Gastric cancer	Diagnostic	NCT05901376
miR-199a	Gastric cancer	Diagnostic	NCT05901376
miR-22	Gastric cancer	Diagnostic	NCT05901376
Sha-miR-71a	Bilharzial BlC	Diagnostic, prognostic	NCT05697224

in translational repression. This occurs either through disruption of the translational machinery (leading to truncated proteins) or by sequestering mRNAs into cytoplasmic P-bodies. Within P-bodies, mRNAs may undergo degradation by exonucleases or deadenylation by poly(A)-specific nucleases.[56]

The ability to regulate miRNA expression in vivo holds promise as a foundation for developing novel therapies. Several strategies have already been established to modulate miRNA levels. To increase miRNA activity, researchers can employ: (i) miRNA mimics, (ii) small synthetic double-stranded molecules that are processed into functional miRNAs, (iii) miRNA expression vectors to induce cellular miRNA production, or (iv) direct delivery of mature miRNAs. Conversely, to suppress miRNA activity, antagomirs and miRNA sponges synthetic sequences complementary to target miRNAs can be used to block their interaction with endogenous mRNA. Given that miRNAs play key roles in cancer-related processes such as cell proliferation, apoptosis, differentiation, invasion, metastasis, and tumorigenesis, these regulatory approaches may offer significant therapeutic potential.[57]

Like miRNAs, siRNAs act as post-transcriptional regulators and have been investigated for their therapeutic potential in various diseases, including cancer, hepatitis, and metabolic and genetic disorders. In recent years, siRNAs have garnered significant attention due to their potential clinical applications. Several miRNA- and siRNA-based therapies are currently under evaluation in clinical trials, and three Food and Drug Administration (FDA) approved RNA interference (RNAi) drugs based on siRNA are available for targeting primary hyperoxaluria type 1, acute hepatic porphyria, and transthyretin-mediated amyloidosis.[56] Hence, diagnostic applications of small non-coding RNAs, such as miRNAs, which are stable in biofluids (blood, saliva, urine) and serve as non-invasive biomarkers for various cancers, including glioblastoma (e.g., miR-21) and breast cancer (e.g., miR-155). siRNAs are also used in liquid biopsies for detecting oncogenic mutations. piRNAs, though less studied, show promise in early-stage cancer detection (e.g., piR-823 in colorectal cancer). Therapeutic applications are a significant feature of ncRNA, where miRNA mimics (e.g., miR-34a) and antagomirs (anti-miRs) are utilized in clinical trials for cancer and cardiovascular diseases, respectively. Furthermore, siRNA-based drugs (e.g., Patisiran for amyloidosis) were used to leverage RNAi to silence disease-causing genes.[58]

Understanding tRNA modifications as medium ncRNAs is highly significant because even minor disruptions in this balance, such as the absence of a single tRNA, can lead to tissue degeneration or death. Recent studies have shown that tRNA expression can be post-transcriptionally regulated by microRNAs (miRNAs).

Additionally, dysregulation in tRNA expression, misacylation by aminoacyl-tRNA synthetases, and tRNA hypomodification can all impact gene expression, potentially contributing to diseases such as cancer, neurodegenerative disorders, and metabolic conditions. Given that aberrant tRNA levels can modulate gene expression, deciphering the mechanisms controlling tRNA expression and the consequences of its dysregulation is crucial. Unraveling these processes could pave the way for novel therapeutic strategies, enabling targeted and personalized treatments for various diseases. [59]

Small RNAs derived from tRNAs have garnered significant interest as potential biomarkers. Several studies have identified circulating tRNA-derived fragments (tRFs) as diagnostic tools for various diseases, including epilepsy, clear cell renal cell carcinoma, and gastric cancer (GC). In line with these findings, Wang et al observed significantly reduced plasma levels of specific tRFs—tRF-GluCTC-003, tRF-GlyCCC-007, tRF-GlyCCC-008, tRF-LeuCAA-003, tRF-SerTGA-001, and tRF-SerTGA-002—in patients with early breast cancer (EBC).[60]

The authors proposed that these 5′-derived tRFs could serve as potential biomarkers for the *in situ* diagnosis of EBC, though further validation with a larger sample size is required. In this line, Zhang et al. reported that tRF-3019a is overexpressed in GC and directly targets the tumor suppressor gene *FBXO47* (F-box protein 47). Their findings revealed that tRF-3019a promotes GC malignancy by suppressing *FBXO47*, highlighting its critical role in GC progression. These results suggest that tRF-3019a may function as an oncogenic factor, positioning it as a promising diagnostic biomarker or therapeutic target for GC.[61] Beyond GC-associated tRFs, Green et al also observed a significant downregulation of tRF-3003a in osteoarthritic cartilage, implicating its potential role in osteoarthritis (OA).[56,62]

Dysregulation of rRNA biogenesis kinetics, for example, in breast cancer (BC), is linked to elevated levels of intermediate rRNA species that are less efficient in mRNA translation. Recent studies suggest a silencing mechanism that inhibits pre-rRNA expression when rRNA processing is defective. Notably, ribosomes exhibit structural and functional heterogeneity, and their varying affinities for different mRNAs represent an emerging mechanism of translational control in gene expression. However, rRNA synthesis can be disrupted at multiple stages, including alterations in rDNA copy number, impaired rDNA transcription, and errors in rRNA processing and modification, ultimately leading to defective ribosome assembly. Such dysregulation may promote aberrant protein aggregation, thereby disrupting proteostasis.[56]

In this context, diagnostic applications of medium ncRNAs, such as tRFs, have been identified in the dysregulation of neurodegenerative diseases and cancers, serving as novel biomarkers. Also, snoRNAs (e.g., SNORD78 in lung cancer) correlate with tumor progression. [63] On the other hand, therapeutic applications of modified tRNAs are explored for suppressing nonsense mutations in genetic disorders. snoRNA-targeting therapies are also being tested for ribosomopathies and cancers.[64]

Linear lncRNAs are currently being explored in clinical trials as noninvasive biomarkers, detectable in circulating blood or urine. Their expression levels can indicate disease severity or reveal specific patterns in certain types of cancer. For example, Htoo et al demonstrated that elevated PCA3 lncRNA levels in urine correlate with prostate cancer progression. Similarly, Kumarswamy et al identified LIPCAR lncRNA in plasma as a potential prognostic biomarker for cardiovascular mortality. Additionally, Lorenzen et al showed that circulating TAPSAKI lncRNA levels could predict mortality in patients with acute kidney injury.[56] To disrupt lncRNA activity, several strategies can be employed: (i) Transcriptional modulation: Altering the promoter activity of the lncRNA-coding region to suppress transcription. (ii) RNAi and antisense targeting: Using siRNAs, shRNAs, or modified antisense oligonucleotides (e.g., gapmers) to silence lncRNAs, which can lead to epigenetic derepression and subsequent activation of sense genes. (iii) Aptamer-based disruption: Employing aptamers to bind specific lncRNA structural domains, interfering with their interactions with binding partners. (iv) Ribozyme-mediated degradation: Utilizing ribozymes to cleave and degrade target lncRNAs. (v) Small-molecule/peptide inhibitors: Designing synthetic molecules or peptides to block lncRNA interactions with regulatory factors. To enhance or restore lncRNA expression to normal levels, strategies leveraging clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology can be employed. Specifically, a catalytically inactive Cas9 (dCas9) fused to the transcriptional activator domain VP64 can be used to activate a target promoter. However, plasmid or viral vector-based approaches may yield ambiguous results, as some lncRNAs influence gene expression within their native genomic contexts. While lncRNAs hold significant promise as therapeutic agents, several challenges hinder their full understanding and application. These include the lack of humanized models or organoid cultures, the involvement of lncRNAs in diverse molecular mechanisms, and their multifunctional roles.[65] However, Diagnostic applications of lncRNAs are determined by HOTAIR (in breast cancer) and MALAT1 (in lung cancer) as prognostic markers.[66] Linc-p21 is also associated with chemoresistance in multiple types of cancer. As a therapeutic target, ASO targeting lncRNAs (e.g., targeting NEAT1) is being evaluated in glioblastoma. Moreover, CRISPR-based lncRNA editing is being investigated for epigenetic modulation.[67]

Techniques such as RNAi utilize a variety of interfering RNAs to silence disease-causing or mimic silenced/haploinsufficient genes selectively to restore regular gene expression.[2] In addition, the development of delivery systems, including nanocarriers, has further facilitated the efficient delivery of these RNA molecules to target cells, thereby opening new avenues for precise and personalized medicine.[68]

Overall, ncRNA-based systems have been explored in several syndromes, and many have progressed to clinical trials. However, to make an RNA product suitable for biomedical applications, specific conditions must be met, and RNA purity, stability, and bioactivity must be verified. So, in the following, a viewpoint on the key challenges and advanced approaches for the broad diagnostic and therapeutic applications (Fig. 4) of ncRNA is introduced.

Diagnostic Advancements through Nanomedicine

One of the main areas where nanomedicine is making significant advances is in diagnosis. For instance, nanosensors are being developed to detect diseases at an early stage.[9] In addition, nano-based sensors/biosensors can be designed to detect specific biomarkers or abnormal cellular activities with remarkable accuracy, enabling the early detection of conditions such as cancer, diabetes, infectious diseases, and neurological disorders.[69]

It has been verified that ncRNAs exhibit remarkable stability in whole blood, which can be utilized as novel biomarkers for specific syndromes, including cancers (Fig. 5).[70] Among ncRNAs, miRNAs have been studied

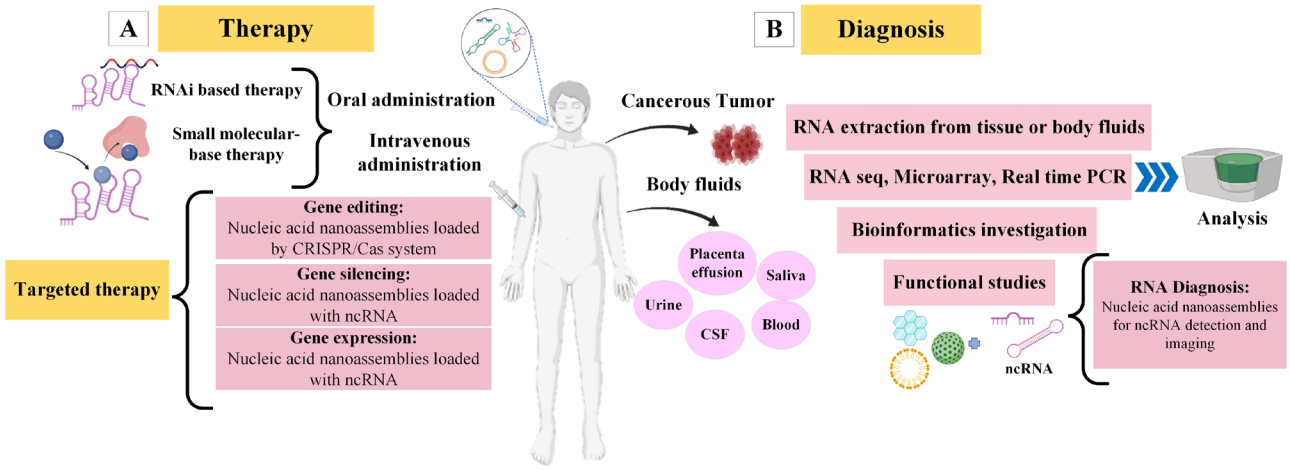

Fig. 4. ncRNA is used as a diagnostic and therapeutic indicator of cancer. (A) ncRNA-based treatments might target the ncRNA by exploiting RNAi therapeutic molecules and/or using tiny molecular suppressors of their protein associates. These helpful paths could be proper for oral or intravenous administration. Additionally, targeted therapies such as gene editing, gene silencing, and gene expression via nucleic acid nanoassembly have enhanced the chances of RNA therapy. (B) Tumor cells and various body fluids are used for diagnosis. ncRNA isolation and detection. The identification of ncRNAs associated with cancer has been facilitated by the advancement of several high-performance expression analysis technologies. Nucleic acid nanoassemblies for ncRNA detection and imaging may be employed for cancer identification and prognosis, and can serve as therapeutic biomarkers.

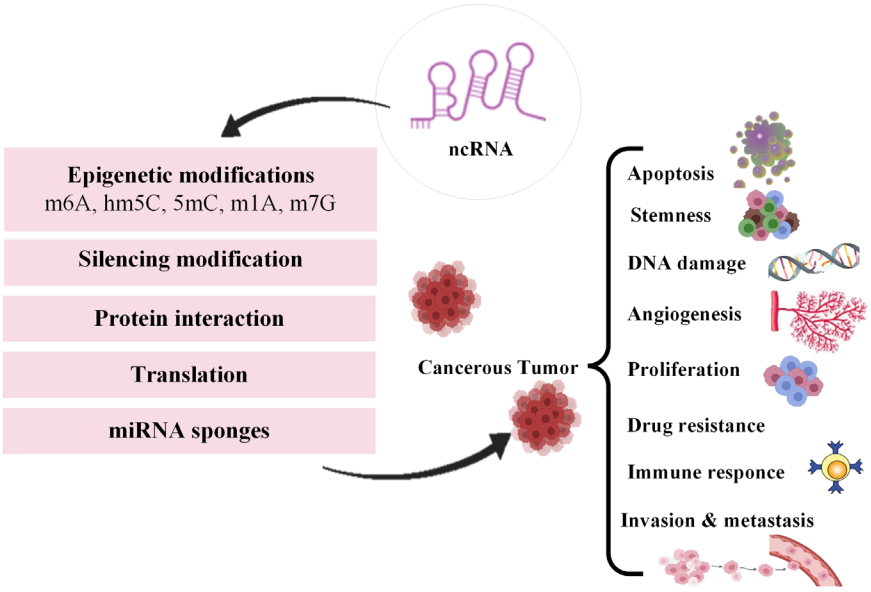

Fig. 5. RNA-based therapeutic in cancer. ncRNAs via modification can be effective in the prevention of proliferation, metastasis, angiogenesis, drug resistance, DNA damage, and invasion.

in most studies, and they are involved in many biological processes.[71-74] For instance, most liver cancer-associated miRNAs have been investigated by Shi et al. in a clinical system.[75] Based on their investigation, four miRNAs were up-regulated and five miRNAs were down-regulated in liver cancer tissues.

The integration of nanomedicine with imaging modalities has revolutionized medical imaging, offering high-resolution images for precise diagnosis.[76] For this case, NPs are being used as contrast agents in medical imaging techniques such as MRI and CT scans, allowing for more accurate and detailed visualization of tissues and organs.[77]

Another thrilling application of nanomedicine in diagnostic systems is the improvement of liquid biopsy tests.[78] These tests can be applied to nanoscale technologies to detect and discover circulating tumor cells or fragments of tumor DNA in the circulation.[79,80]

Nanomedicine has revolutionized liquid biopsy procedures by improving the sensitivity and specificity of ncRNA detection. Liquid biopsies, which analyze biomarkers in bodily fluids such as blood, rely on nanotechnology to isolate microRNAs and lncRNAs from complex biological matrices. Liquid biopsies offer a non-invasive alternative to traditional tissue biopsies and can provide valuable information about the presence, progression, and treatment response of cancer. NPs, such as gold nanoparticles and magnetic beads, functionalized with antibodies or oligonucleotides, enable the selective capture of ncRNAs even at low concentrations. For example, a study by Wang et al demonstrated that silica-coated magnetic nanoparticles efficiently extracted exosomal microRNAs from plasma, enhancing detection limits by 100-fold compared to conventional methods.[81] Moreover, gold nanoparticles and quantum dots enhance extraction efficiency by selectively binding to ncRNAs, enabling their isolation even at minimal concentrations.[82] This approach minimizes sample loss and improves diagnostic accuracy, particularly in early-stage cancers where ncRNA levels are typically low.

Furthermore, advanced nanoplatforms for ncRNA enrichment are also introduced. Nanotechnology-based platforms, such as exosome isolation kits employing antibody-coated nanoparticles, have been instrumental in enriching tumor-derived exosomes containing ncRNAs. Exosomes, which carry ncRNAs, are crucial for cancer diagnostics but are challenging to isolate due to their small size. Silicon-based nanowires and polymer nanoparticles have demonstrated high affinity for exosomal ncRNAs, facilitating their purification from complex biofluids.[82] A notable example is the use of lipid-based nanoparticles to extract exosomal lncRNAs in cancer patients, enabling early diagnosis with high accuracy. These nanoplatforms not only enhance yield but also preserve RNA integrity, ensuring reliable downstream analysis.[83]

The integration of nanomedicine in liquid biopsies holds immense potential for personalized medicine, particularly in oncology. For example, a study by Dogra et al[84] demonstrated that nanoparticle-based enrichment of miR-155 in the blood of lung cancer patients correlated with treatment response, highlighting its prognostic value. Despite these advances, challenges such as standardization and biocompatibility remain. Future research should focus on optimizing nanoparticle designs for clinical scalability while minimizing off-target effects. As nanomedicine continues to evolve, its role in liquid biopsy-based ncRNA diagnostics is expected to expand, paving the way for earlier and more accurate disease detection.

To date, electrochemical, optical, and electromechanical systems (including mass, surface stress, and resonance) based on various biological responses have been developed using DNA-based biosensors for the recognition of cancer-associated biomarkers. Among several DNA-based biosensors, electrochemical ones offer an outstanding capacity for biomarker detection due to their striking benefits, including ease, rapidity, cost-effectiveness, and the opportunity for miniaturization.[85,86] Most electrochemical assays were established to identify overexpressed oncogenic miRNAs by enhancing the monitoring of the signal from cancer cells and comparing it to that from healthy cells. Cancer suppressor miRNAs, which are underexpressed in cancer cells, are typically not targeted because their levels are frequently below the detection limits of the assays. Therefore, recently, more sensitive and specific systems have been developed for miRNA determination.[87-90] In this case, a sensitive and specific technique for the electrocatalytic detection of target miRNA (miR-107) by gold-loaded nanoporous superparamagnetic magnetic nanocubes (Au-NPFe_2O_3NC) has been developed. The proposed system was employed to determine miR-107 levels in cancer cell lines with remarkable reproducibility and high specificity. RT-qPCR was applied as a standard method. The obtained system displayed a high translational potential for monitoring miRNAs in biological fluid samples.[91]

Therapeutic Innovations with NPs

Nanomedicine is updating the field of therapeutics by supporting targeted drug delivery and personalized medicine.[92,93] NPs, such as liposomes and polymeric NPs as efficient nanocarriers, can be engineered and commonly applied to encapsulate drugs and deliver them directly to the site of action.[94,95] This targeted approach lessens side effects and enriches the efficacy of the treatment. NP-based therapies can be functionalized with ligands that specifically bind to receptors on diseased cells, further enhancing drug delivery and reducing off-target effects.[50,96] Additionally, nano-based therapies have shown promising results in battling multidrug-resistant

pathogens and overcoming biological barriers.

Nanomedicine has shown great promise for cancer treatment.[97,98] NP-based therapies, such as gold NPs and carbon nanotubes, can selectively target cancer cells while maintaining healthy tissues.[99,100] These NPs can be loaded with chemotherapy drugs or therapeutic agents and delivered directly to the tumor site, maximizing the treatment's effectiveness.[101] Additionally, nanorobots are being developed to navigate through the bloodstream and deliver drugs with precision, minimizing systemic toxicity.[17,102]

Some types of NPs have been discovered for ncRNA delivery, including liposomes, polymeric NPs, dendrimers, and inorganic NPs. NPs employed in the delivery of therapeutic ncRNAs for FDA-approved and clinical-stage candidates exhibit diverse structural characteristics tailored to enhance stability, targeting, and cellular uptake.

Liposomes, composed of lipid bilayers, are one of the most extensively investigated NPs for ncRNA delivery.[103,104] They can be applied as encapsulated agents for both hydrophilic and hydrophobic ncRNAs, providing protection and controlled release. In this line, LNPs, such as those used in Patisiran (ONPATTRO®), feature ionizable lipids, phospholipids, and cholesterol to deliver siRNA, leveraging their biocompatibility and endosomal escape capabilities. PEG-lipids were used to encapsulate siRNA, enabling endosomal escape and hepatic delivery.[105] Also, LNPs modified with targeting ligands (e.g., GalNAc for hepatocyte-specific delivery) are being verified for miRNA therapeutics in cancer and metabolic diseases.[106]

Polymeric NPs, on the other hand, are composed of biocompatible polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG). These NPs can be easily modified to improve stability, targeting, and release kinetics. Polymeric NPs, including PLGA and polyethyleneimine (PEI), offer controlled release and cationic surfaces for nucleic acid complexation. In clinical trials, novel formulations like cyclodextrin-based polymers (e.g., CALAA-01) and gold NPs functionalized with oligonucleotides demonstrate improved biocompatibility and tumor targeting.[107]

Dendrimers, with their highly branched structure, offer a high payload capacity and efficient cellular uptake. Inorganic NPs, such as gold NPs and quantum dots, offer unique optical and magnetic properties that can be exploited for imaging and therapeutic purposes.[108-110] Additionally, exosome-based systems leverage natural vesicular structures for enhanced biodistribution. Key modifications, such as PEGylation and ligand conjugation (e.g., GalNAc for hepatocyte targeting), further refine pharmacokinetics and tissue specificity. These advancements highlight the critical role of nanoparticle design in overcoming biological barriers for effective ncRNA therapeutics.[105]

Furthermore, advancements in extracellular vesicle (EV)-based NPs and peptide-derived carriers offer promising alternatives with reduced immunogenicity. Despite challenges such as scalability and off-target effects, the integration of smart NPs responsive to pH, enzymes, or redox conditions holds promise for precision therapy. Collectively, these innovations underscore the pivotal role of nanotechnology in realizing the clinical potential of ncRNA therapeutics. Besides the potential of NP-based ncRNA therapeutics, several challenges and boundaries should be addressed carefully.[111,112] One of the main worries is the stability and degradation of ncRNAs within the NPs.[113] Nucleases and other enzymes introduced into the biological milieu can degrade ncRNAs, leading to reduced therapeutic efficacy.[104,114] Chemical modifications and encapsulation strategies within protective matrices have been applied to overcome this issue.[115] Another challenge is achieving targeted delivery of ncRNAs to specific cells or tissues.[116] While surface modification of NPs with targeting ligands can enhance specificity, further optimization is still needed to ensure efficient and selective delivery. In addition, the immunogenicity and toxicity of NPs should be carefully evaluated to diminish adverse effects.

To improve the effectiveness of NP-based ncRNA therapeutics, several approaches have been discovered.[113,116,117] NPs along with ligands or antibodies, can boost cellular uptake and targeting by surface modification.[118-120] Therapeutic agents such as small molecules or proteins integrated with ncRNAs can enrich the effectiveness.[121,122] Mixture therapy attitudes, where several ncRNAs or therapeutic compounds are conveyed simultaneously, have also exposed beneficial consequences. These policies aim to overcome the challenges of diseases by targeting multiple pathways or molecular targets simultaneously.

Recent innovations in NP-based ncRNA therapeutics have confirmed their potential in numerous syndromes.[123-125] For instance, NP-based delivery of tumor suppressor ncRNAs has revealed promising potential in animal studies.[126,127] Correspondingly, in Alzheimer's and Parkinson's, NP-mediated delivery of neuroprotective ncRNAs has displayed neurorestorative impacts.[115] Some clinical evaluations are presently ongoing to assess the safety and efficiency of NP-based ncRNA therapeutics in humans, emphasizing their promising potential in the healthcare system.

Looking ahead, NP-based ncRNA therapeutics play a significant role in personalized medicine and disease-specific targeting.[128-130] With advancements in nanomedicine and our understanding of ncRNA biology, it is possible to design NPs that can selectively deliver ncRNAs to specific cell types or disease sites.[131,132] This opens up new avenues for precision medicine, where therapies can be tailored to individual patients based

on their genetic profile and disease characteristics. Furthermore, NP-based ncRNA therapeutics can also be employed in gene editing and gene therapy applications, offering potential cures for genetic disorders.

Overall, therapeutic advances with NPs for ncRNA have developed the field of molecular medicine. NPs provide unique advantages in terms of stability, protection, and targeted delivery of ncRNA therapeutics. A comparative analysis of nano-delivery systems for ncRNAs reveals distinct advantages and limitations based on their design and composition. LNPs, especially liposomes, are widely used due to their high biocompatibility and efficient encapsulation of ncRNAs like siRNA and miRNA; however, they may suffer from instability and rapid clearance in vivo.[70] Polymeric NPs, such as PLGA or chitosan, offer controlled release and protection against enzymatic degradation, but can exhibit cytotoxicity and low transfection efficiency.[133] Inorganic NPs, such as gold or silica-based systems, provide tunable surfaces for functionalization and enhanced cellular uptake; however, their potential long-term toxicity and poor biodegradability remain concerns.[134] Each system thus presents trade-offs between delivery efficiency, safety, and therapeutic applicability.

Emerging nano-delivery platforms, such as exosomes and hybrid systems, aim to overcome these limitations by leveraging natural biocompatibility and targeting capabilities. Exosomes, as endogenous vesicles, minimize immune responses and enhance the tissue-specific delivery of ncRNAs, but their large-scale production and heterogeneity pose challenges.[135] Hybrid systems combining lipids, polymers, or inorganic materials

attempt to synergize the benefits of multiple approaches, improving stability and targeting precision.[136] However, the complexity of fabrication and potential batch-to-batch variability may hinder clinical translation. The choice of delivery system ultimately depends on the specific ncRNA (e.g., siRNA, lncRNA, or circRNA), desired pharmacokinetics, and the target tissue, necessitating further optimization for personalized therapeutic applications.

Despite the challenges and limitations in therapeutic strategies, ongoing research in nanomedicine is paving the way for the development of safe and effective NP-based ncRNA therapeutics. With further optimization and clinical validation, these innovative approaches have the potential to transform the treatment landscape for various diseases, bringing us closer to the realization of personalized and precision medicine. In this context, the efficiency of treatment achieved through the transfer of ncRNA using nano-delivery systems for cancer treatment is represented in Table 2.

Commercialization opportunities, overcoming obstacles, and conclusion

The convergence of ncRNA and nanomedicine presents substantial commercialization opportunities in the healthcare industry. Although traditional detection methods for ncRNAs, such as qRT-PCR, northern blotting, and microarray, are widely applied, they have some limitations that discourage their use, including laborious techniques, long processing times, sample size requirements, varying sensitivities of the kits and instruments, and false-positive results. In terms of technical aspects, analytical companies, utilizing sensor and biosensor devices, can develop non-invasive tests that use nano-sensors/biosensors to identify ncRNAs as biomarkers, thereby providing accurate and timely disease detection. Pharmaceutical companies, alternatively, can capitalize on the targeted drug delivery systems offered by nanomedicine, improving drug efficacy and controlled release. This can be achieved by constructing more stable, longer-lasting, and less toxic antisense or mimic oligonucleotides to downregulate or upregulate a specific ncRNA, respectively, for therapeutic purposes.

Advances in RNAi technologies, such as siRNA and miRNA-based therapies, have led to FDA-approved treatments, including Patisiran, for hereditary transthyretin amyloidosis. Nanocarriers, such as LNPs and polymeric nanoparticles, enhance delivery efficiency, reducing off-target effects and improving bioavailability.

Companies like Alnylam and Moderna are leveraging these innovations, with increasing investments in RNA-nanomedicine hybrids for the treatment of cancer, cardiovascular diseases, and rare genetic disorders. Additionally, diagnostics utilizing exosomal ncRNAs as biomarkers for early cancer detection present lucrative opportunities for biotechnology firms. However, scalability, manufacturing consistency, and regulatory hurdles remain key challenges to widespread adoption.[148]

While the prospects are promising, several challenges must be addressed for effective commercialization to occur. Safety concerns surrounding the use of nanomaterials, regulatory frameworks, and manufacturing scalability are among the key hurdles. Stability issues, immune system clearance, and inefficient tissue targeting limit therapeutic efficacy. Recent innovations, such as exosome-based carriers, offer improved biocompatibility and natural tropism for specific cells, enhancing delivery precision.

Clinical trials, such as those investigating exosome-delivered miR-34a for solid tumors (NCT03608631), highlight both promise and pitfalls, e.g., variable patient responses and manufacturing complexities. Furthermore, regulatory agencies demand rigorous safety assessments, necessitating standardized protocols for nanoparticle characterization. Collaborative efforts between academia, industry, and regulators are essential to address these challenges.

Nanorobotics holds immense potential in the field of ncRNA therapeutics and diagnostics, yet several challenges must be addressed for clinical translation. One

Table 2. Summary of cancer treatment with the delivery of ncRNA therapeutics through nano-delivery systems

ncRNA	Delivery system	Cancer type	Therapeutic impact	Ref.
MT1DP	Folate-modified liposome NPs	NSCLC	Raised erastin-induced ferroptosis by augmentation of Malondialdehyde and ROS levels, enhancement of intracellular Ferrous iron concentration, and reduction of glutathione levels	137
MDC1	Thermosensitive magnetic cationic liposomes	Cervical cancer	Magnetic cationic liposomes cause Overwhelmed with definite adverse responses and improved the inhibition of cell growth related to cervical cancer	138
LINC01257	Lipid NPs	AML	LNPs lessen cell count after 48 h of treatment, damage Kasumi-1 cell proliferation without disturbing healthy PBMCs	109
NRCP	DOPC nanoliposomes	Ovarian cancer	Considerably diminished tumor growth NRCP playing as a middle-associated partner between STAT1 and RNA polymerase II, leading to amplified expression of downstream target genes	139
Malat1	Liposomal spherical nucleic acid constructs	Lung adenocarcinoma	Boosted the tumor suppressor, interferon-induced protein with IFIT2	140
LCDR	NT-NPs	Lung adenocarcinoma	siLCDR/AUTP multiplexes precisely target the nucleus to suppress the effective gene, declining cancer growth of patient-derived xenografts of lung adenocarcinoma	141
CCAT1	CSNPs	Colorectal cancer	Expressively limited HT-29 tumor growth, with suitable biosafety and biocompatibility in the animal model	142
lncAFAP1-AS1	PDSA polymer NPs	Triple-negative breast cancer	Silencing lncAFAP1-AS1 expression and scavenging the elevated GSH, leading to synergistic reversal of radioresistance. Enhanced the radiosensitivity and improved the radiotherapy effect	13
DANCR	RGD-PEG-ECO NPs	Triple-negative breast cancer	Meaningfully limited the survival, invasion, migration, and proliferation of the TNBC cell lines	38
ANRIL	DTBP-3NP-siANRIL NPs	Hepatocellular carcinoma	Signaling the expression of miR-203a and its following genes and augmented the ratios of NK cells and T cells	15
MALAT1	s-PGEA-FA NPs	Esophageal squamous cell carcinoma	Effectively inhibiting esophageal squamous cell carcinoma development	143
MEG3	PuPGEA NPs	Hepatocellular carcinoma	Effectively inhibiting tumor growth and inducing tumor necrosis	21
MEG3	CNC@CB8 @PGEA NPs	Hepatocellular carcinoma	Effectively inhibiting HCC tumor growth	117
MEG3	PAMAM-PEG-EpDT3 NPs	CRPC	Noteworthy anti-CRPC outcome, both in the animal model and in vitro study	22
MALAT1	ASO-Au-TAT NPs	Lung cancer	Reducing MALAT1 expression level, decreasing migration capability in vitro and reducing metastatic tumor nodule formation in an animal study	23
OUM1	ICG-MOF-RGD NPs	UM	Conquers UM proliferation and metastasis and enhances cisplatin sensitivity in UM cells	25
MALAT1	Single wall carbon nanotube (SWCNT)-antiMALAT1	MM	Inducing DNA damage and cell apoptosis in vivo	36
LINC00589	PMSNs	GC	Conquer the metastatic ability of GC cells in an animal model and in vitro study	45
miR-122	Multivalent rubber-like RNA NPs	Liver cancer	Silencing of drug exporters and oncogenic proteins, as well as inhibition of tumor growth	46
miR-218	LA-PAMAM	Liver cancer	Diminished tumor progression and amended liver histological features	41
miR-451	calcium carbonate NPs	Bladder cancer	Suppression of multidrug resistance and augmented growth of intracellular Adr with anticancer properties	42
miR-199a-3p	Omentum-derived exosomes	Ovarian cancer	Inhibition of cell proliferation and invasion	27

Table 2. Continued

ncRNA	Delivery system	Cancer type	Therapeutic impact	Ref.
miR-let-7c-5p	SiO_2-polyethyleneimine NPs	Cervical cancer	Suppression of cell proliferation and migration	144
miR-200c	CXCR4-targeted polymeric poly-Lglutamic acid-coated NPs	Colon cancer	Enhanced immune responses against tumors	29
miR-139-5p	R9 modified with ^{125}I-labeled RGD and Ce6	Cancer in general	Boosted the radiotherapy sensitivity with low toxicity	31
let-7i	Nano-graphene oxide platform	Cancer in general	Retreated intracellular drug and improved photothermal therapy with chemical agents	32
miR-532-3p	PLGA-PEG-VB12 NPs	Gastric cancer	Mitochondrial impairment, amplified apoptosis, and limitation of cell proliferation	51
miR-181a	GDY-CeO2 nanozymes	Esophageal cancer	Improvement of tumor hypoxia and radiation-induced DNA damage, and inhibition of tumor growth	52
miR-15a and miR-16–1	Cationic PEGylated niosomes	Prostate cancer	Augmented apoptosis of tumor cells	34
miR-320	a combination of TAT-coated SLNs with peptides containing the NGR motif	Head and neck cancer	Declined Oxa-associated toxicities and high antitumor value	145
miR-181a	ZIF-8 nano-complexes	Rectal cancer	Improved radiosensitivity, limited proliferation, lessened migration, and boosted apoptosis	146
miR-30a-5p	MMNs	Ocular melanoma	Enriched pro-inflammatory anticancer immunity against skin cancer	147
MRX34 (miR-34a mimic)	Liposome	Solid tumor	Phase I terminated	NCT02862145
Atu027	Liposome	Solid tumors	Phase I completed	NCT00938574
siG12D LODER	PLGA matrix	LAPC	Phase I completed Phase II	NCT01188785 NCT01676259
TKM-080301	LNP	NET and ACC HCC Liver cancer	Phase I/II completed Phase I/II completed Phase I completed	NCT01262235 NCT02191878 NCT01437007
EphA2 siRNA	DOPC neutral liposome	Advanced or recurrent solid tumor	Phase I	NCT01591356
NU-0129	Gold nanoparticle	Glioblastoma	Phase I completed	NCT03020017
ALN-VSP02	Co-delivery of two siRNAs with LNP	Advanced solid tumor with liver involvement	Phase I completed	NCT00882180
CALAA-01	Cyclodextrin nanoparticles targeting transferrin receptor	Solid tumor	Phase I terminated	NCT00689065
DCR-MYC	LNP	Solid tumor, multiple myeloma, or lymphoma HCC	Phase I terminated Phase I/II terminated	NCT02110563 NCT02314052

NSCLC, non-small-cell lung cancer; AML, acute myeloid leukemia; CRPC, Castration-resistant prostate cancer; UM, Uveal melanoma; MM, Multiple myeloma; GC, gastric cancer.

major obstacle is the precise delivery of ncRNA molecules to target cells without degradation or off-target effects. Nanorobots equipped with molecular recognition systems can enhance specificity by binding to overexpressed biomarkers on diseased cells, thereby improving the accuracy of therapeutic interventions. Additionally, advancements in biocompatible materials and propulsion mechanisms, such as magnetic or enzymatic propulsion, are overcoming biological barriers, including immune clearance and vascular dynamics.[149] Nanorobotics integrated with ncRNA-based therapies offers unprecedented control over gene regulation and disease detection. For instance, nanorobots carrying CRISPR-Cas9 and guide RNA can perform precise gene editing,

while those loaded with fluorescent reporters enable real-time imaging of tumor-associated ncRNAs. Furthermore, adaptive nanorobots can respond to microenvironmental cues (e.g., pH, enzymes) to release payloads selectively, minimizing systemic toxicity. Such innovations bridge the gap between ncRNA biology and clinical applications, paving the way for personalized medicine.[150]

Despite progress, scalability and long-term safety remain hurdles in nanorobotic-ncRNA systems. Manufacturing nanorobots with uniform properties at scale requires sophisticated techniques, such as DNA origami or 3D nanoprinting. Immunogenicity and unintended biodistribution also pose risks, necessitating rigorous preclinical testing (Sharma et al., 2023). Computational modeling and AI-driven design are being employed to predict the behavior of nanorobots in vivo, thereby optimizing their efficacy and safety profiles. Addressing these challenges will be critical for regulatory approval and clinical adoption.[151]

The convergence of nanorobotics and ncRNA nanomedicine is revolutionizing therapeutic and diagnostic paradigms. By overcoming delivery barriers, enhancing precision, and improving biocompatibility, nanorobots are unlocking new avenues for treating cancers, genetic disorders, and infectious diseases. Future research should focus on scalable fabrication, smart responsiveness, and rigorous clinical trials to translate these technologies from bench to bedside. As the field advances, interdisciplinary collaboration will be key to harnessing the full potential of nanorobotics in ncRNA medicine.

Exosomes have also emerged as promising carriers for ncRNAs due to their biocompatibility, low immunogenicity, and ability to cross biological barriers. These nanoscale vesicles facilitate intercellular communication by transferring functional ncRNAs to target cells, modulating gene expression, and cellular functions. Their endogenous origin minimizes toxicity and enhances stability, making them superior to synthetic nanoparticles for therapeutic delivery. Additionally, exosomes can be engineered to enhance targeting efficiency, allowing for the precise delivery of ncRNA-based therapeutics in diseases such as cancer and neurodegenerative disorders. Despite their potential, exosome-based ncRNA delivery faces challenges, including low yield during isolation, heterogeneity, and inefficient loading of therapeutic ncRNAs. Advances in nanotechnology have addressed these issues by optimizing isolation techniques (e.g., ultracentrifugation, size-exclusion chromatography) and developing novel loading strategies, such as electroporation and sonication. Surface modification with ligands (e.g., peptides, antibodies) enhances tissue-specific targeting, while genetic engineering of parent cells allows for customized exosome production.

Furthermore, integrating exosomes with synthetic nanoparticles (hybrid systems) improves payload capacity and pharmacokinetics, overcoming limitations in clinical scalability. Hence, Exosome-based carriers represent a transformative platform for ncRNA delivery, bridging the gap between nanomedicine and clinical applications. While challenges remain in standardization and large-scale production, ongoing advancements in bioengineering and nanotechnology are paving the way for scalable, targeted therapies. Additionally, translating scientific discoveries into marketable products requires substantial investments in developing basic research, conducting clinical trials, and protecting intellectual property.

Nanomedicine and ncRNA represent cutting-edge fields with tremendous potential in the field of healthcare. The complex regulatory roles of ncRNA and the precision of nanotechnology hold promising solutions for the development of innovative diagnostic and therapeutic approaches. By leveraging the power of these technologies, we can advance disease detection, enhance treatment outcomes, and pave the way for a more personalized and efficient healthcare system.

In conclusion, the potential synergy derived from combining ncRNA and nanomedicine offers a pathway to address unmet medical needs. By driving scientific advancements, fostering collaborations, and embracing commercialization opportunities, we can unlock the full potential of these cutting-edge technologies and shape the future of healthcare systems. Further advancements in this interdisciplinary field will contribute to the progression of precision medicine and patient satisfaction.

Authors' Contribution

Conceptualization: Kamyar Khoshnevisan.
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Competing Interests

The authors declare no competing interests.

Review Highlights

What is the current knowledge?

- ncRNAs, previously considered 'junk DNA' and insignificant, are now being documented for their remarkably extraordinary regulatory roles in gene expression and various cellular processes.
- Technical aspects and potential of commercializing the design and targeting of ncRNAs using nanocarriers and nano-delivery systems are confirmed.

What is new here?

- The enormous benefits of ncRNA therapies include ease of sequence design and creation, functional flexibility, charge and protection, and the opportunity for patient-specific management.

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