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REVIEW

RNA-Based Therapies in Kidney Diseases

Liang Hu[1,*], Ting Jin[2,*], Ning Zhang[3], Jin Ding[2], Lina Li[3,4]

[1]Department of Urology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang, 321001, People's Republic of China; [2]Department of Gastroenterology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, Zhejiang, 321001, People's Republic of China; [3]College of Medicine, Jinhua University of Vocational Technology, Jinhua, Zhejiang, 321016, People's Republic of China; [4]Faculty of Medicine, Faculty of Chinese Medicine and State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, 999078, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jin Ding; Lina Li, Email jhDingJin@zju.edu.cn; 20221054@jhc.edu.cn

Abstract: Kidney diseases are major global health challenges, affecting over 750 million people worldwide. Despite significant efforts, effective treatment strategies are still insufficient. In recent years, RNA therapeutics have made substantial progress, and an increasing number of nucleic acid-based therapies have been approved, showing potential for treating various diseases (including kidney diseases). These therapies can target proteins, transcripts, and genes that were previously considered "undruggable", allowing for the regulation of their expression and the expansion of therapeutic targets. Among RNA therapeutics, mRNA-based therapies are particularly promising because they can rapidly express therapeutic proteins, along with their design flexibility and potential to target previously inaccessible disease mechanisms. This review discussed various RNA-based strategies for developing new treatments, including antisense and RNA interference technologies, mRNA-based approaches, and CRISPR-Cas-mediated genome editing. Additionally, we highlighted the opportunities and challenges associated with the widespread application of these therapies in kidney disease treatment.

Keywords: RNA-based therapies, mRNA therapy, kidney diseases

Introduction

Kidney disease is a complex disease characterized by high morbidity and mortality, affecting over 750 million individuals worldwide and representing a significant global public health challenge.[1] Recent studies have highlighted that the prevalence of chronic kidney disease (CKD) is increasing globally, becoming one of the leading risk factors for mortality worldwide.[2] Although numerous studies have been conducted in recent years aimed at enhancing our understanding of kidney diseases, current research is still insufficient to elucidate the specific mechanisms involved and develop effective treatment strategies.[3] Furthermore, emerging challenges (such as population aging, obesity, and climate change) are expected to exacerbate the global burden of kidney diseases, underscoring the urgency of addressing these issues.[4,5] Consequently, there is a pressing need for more comprehensive research to address these existing gaps.

Recent advancements in RNA technology have significantly enhanced various fields (vaccine development, protein expression, etc)., providing a safe and efficient strategy for the expression or inhibition of specific genes. The RNA interference phenomenon, first described in the 1980s as a gene silencing mechanism triggered by double-stranded RNA, lays the foundation for small RNA (siRNA) technology. With breakthroughs made by scientists such as Karikó[6] in nucleoside base modification, mRNA therapy has been gradually established as a cutting-edge and revolutionary treatment strategy. Furthermore, RNA technology encompasses antisense oligonucleotides (ASOs) and nucleic acid aptamers. ASOs consist of specific short, single-stranded DNA or RNA that complementarily bind to target mRNA sequences, interfering with and regulating the expression of mRNA. Since research began in the 1980s, ASOs have demonstrated the potential to alter gene expression and treat genetic diseases, cancer, and viral infections.[7] Nucleic acid aptamers are single-stranded small molecules composed of RNA or DNA, exhibiting high specificity and affinity for their target molecules and thus exerting regulatory effects. Following the invention of the Systemic Evolution of Exponentially

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Enriched Ligands (SELEX) in the 1990s, aptamers with their easy synthesis, stability, and modifiable properties have been extensively studied across various fields, including diagnosis, treatment, and biological detection.[8]

In recent years, the potential of RNA-based therapies in kidney diseases has gained significant attention. Several studies have explored RNA-based therapies for inherited kidney diseases, which are often characterized by a lack of curative therapies. Bondue et al have reviewed RNA-based approaches for inherited kidney diseases, with a focus on the importance of developing efficient delivery vehicles (such as lipid nanoparticles) to protect RNA molecules from degradation and to enhance targeted delivery to kidney-specific cells.[9] Moreover, they have also discussed strategies for improving the targeting of the glomerulus and tubules using antibodies, peptides, and small molecules, which are vital for kidney-targeted therapies.

In addition to inherited kidney diseases, RNA-based therapies have also shown promise in the treatment of acute kidney injury (AKI), a disease associated with high mortality rates. Haddad et al have explored the role of noncoding RNAs (ncRNAs) in the pathogenesis of ischemic AKI.[10] In short, they have discussed how microRNAs, long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) contribute to kidney injury, as well as their potential as biomarkers and therapeutic targets. This review highlighted the need for further exploration of ncRNAs, particularly their application in AKI-targeted therapy.

This review outlined the advantages and classifications of RNA-based therapies, with a focus on the applications and recent advancements of RNA-based therapies in the treatment of kidney diseases. This review aimed to promote research on RNA as a therapeutic agent for kidney diseases and to provide solutions to the challenges posed by insufficient treatment strategies in this area.

The Advantage of RNA-Based Therapies

By now, various RNA-based medications have been identified and applied in numerous areas (such as vaccines, treatments, and diagnostic tools) due to their significant benefits. This review highlighted several important advantages of these innovations compared to conventional therapeutic agents.

Targeting Multiple Genetic Components

The advantages of RNA-based therapy in targeting multiple genetic components are primarily reflected in its wide application range and high efficiency. RNA drugs can target almost any genetic component within cells, including certain targets that remain inaccessible to other technologies, including small molecules and antibodies that are often referred to as “undruggable” targets. For instance, many ncRNAs, especially small RNAs, possess few distinguishing features apart from their RNA sequences. Importantly, ncRNAs significantly outnumber proteins in the human genome[11] playing a crucial role in the pathogenesis of various human diseases.[12–14] Therefore, RNA drugs designed to target these molecules hold enormous therapeutic potential.

Several RNA drugs targeting ncRNAs have been developed and tested, showing promising results. For example, anti-miR21 is a therapeutic RNA drug that targets microRNA-21, which is involved in fibrosis and the progression of various cancers and diseases, including kidney diseases.[15] Additionally, ASOs targeting lncRNAs have been explored for the treatment of kidney diseases, such as the use of ASOs targeting lncRNA KCNQ1OT1 in polycystic kidney disease models.[16] These approaches underscore the significant therapeutic potential of ncRNA-targeting RNA therapeutics in treating various kidney conditions.

Moreover, prior studies have indicated that less than one-third of human proteins are amenable to effective targeting by small molecules.[17,18] Current RNA therapeutics can precisely target these proteins both in vivo and in vitro.[19,20] RNA therapy primarily exerts two mechanistic effects in treating undruggable targets: (1) utilizing coding RNA for protein or antigen expression, and (2) employing ncRNA to bind and regulate mRNA function (such as promoting degradation or inhibiting translation).[21]

Simple and Flexible Development and Manufacturing Process

In 2020, two breakthrough mRNA vaccines were released in quick succession in response to the COVID-19 pandemic, setting a record for the fastest vaccine development.[22–24] Typically, the process of developing new small molecule or

antibody drugs spans several years. However, RNA-based technologies facilitate rapid production due to their uniform action mechanism within cells. Moreover, RNA-based production technology has been optimized for the application of various RNA products. Notably, RNA-based production systems are automated, encompassing synthesis, isolation, and purification processes. A key advantage of mRNA therapeutics is the in vitro transcription (IVT) process, which is relatively simple and adaptable for large-scale manufacturing. The IVT process allows for rapid synthesis of mRNA from a DNA template, providing a scalable and flexible approach for producing therapeutic mRNA molecules. Consequently, RNA-based technology can be prepared for production in a shorter time than traditional pharmaceuticals. Compared with traditional small molecule drugs and protein-based therapies, mRNA therapeutics are faster and developed more easily, involving fewer steps in the production process. For instance, a drug based on siRNA aimed at targeting illness caused by overexpression of a certain gene in a specific organ may also be adapted to treat other ailments within that organ by merely modifying the siRNA sequence, thus facilitating personalized RNA treatment.

Long-Term Impact

Although natural RNA is readily degraded by nucleases, its stability can be significantly enhanced through various modifications during synthesis.[25] One such breakthrough modification involves introducing pseudouridines into mRNA structure, which can stabilize the mRNA, reduce immune activation, and enhance translation efficiency. Moreover, when these RNAs are encapsulated in carriers (such as liposomes), they are effectively protected against nuclease attacks following systemic administration,[26] thereby extending their lifespan. Another remarkable strategy involves the use of self-amplifying mRNA replicons, which can prolong the duration of mRNA drugs or vaccines and enhance immune responses.[27,28]

Recent studies have also emphasized the significant role of miRNAs in the progression of kidney diseases and their potential therapeutic benefits. For instance, miRNA clusters (such as miR-23a/27a/26a) have been proven to ameliorate renal tubulointerstitial fibrosis in diabetic nephropathy, highlighting their application prospects in RNA-based therapies for kidney diseases.[29] Additionally, miRNA-429-3p has been found to play a pivotal role in ferroptosis regulation during CKD, presenting a potential target for therapeutic intervention.[30]

In addition to miRNAs, recent studies have also emphasized the significant roles of lncRNAs in the context of kidney diseases. For example, Xing et al[31] have explored how lncRNAs regulate the fibroblast-to-myofibroblast transition, which is a critical process in renal fibrosis. Similarly, Lin et al[32] have discovered that lncRNA AP001007 protects renal cells from injury in sepsis-induced AKI. Xie et al[33] have identified lncRNA6524 as a key mediator of renal fibrosis through the Wnt/β-catenin signaling pathway. Furthermore, Li et al[34] have demonstrated that the YY1-induced upregulation of lncRNA-ARAP1-AS2 promotes diabetic kidney fibrosis by altering glycolysis. Finally, Yang et al[35] have shown that FTO modulates the m6A modification of lncRNA SNHG14, playing a crucial role in AKI. These findings emphasize the therapeutic potential of targeting lncRNAs in kidney diseases and provide promising new avenues for treatment strategies.

Moreover, recent studies have highlighted the therapeutic potential of certain chemical drugs and natural products in regulating lncRNAs for the treatment of kidney diseases. Luo et al[36] have demonstrated that quercetin improves contrast-induced acute kidney injury (CI-AKI) through the HIF-1α/lncRNA NEAT1/HMGB1 pathway. This study highlighted the therapeutic potential of quercetin in regulating lncRNA NEAT1 to reduce cell injury and apoptosis in CI-AKI. Additionally, as revealed by Xie et al[37] hederagenin (HDG), a natural compound derived from Astragalus membranaceus, alleviates cisplatin-induced AKI by inhibiting the lncRNA-A330074k22Rik/Axin2/β-catenin signaling pathway. These findings suggest that HDG may be used to modulate lncRNA-related pathways in AKI treatment.

No Genotoxic Risk Profile

Compared to DNA therapy, RNA therapy exhibits no significant genotoxic effects. DNA-based therapies involve delivering DNA molecules into cells via viral vectors, which carry the risk of integrating into the genome and inducing mutations. Genotoxicity is typically defined as the ability of a substance to cause genetic damage that leads to mutations, which may result in cancer or other genetic disorders. DNA-based therapies, especially those using integrating viral vectors, have been shown to carry the risk of insertional mutagenesis, where the inserted DNA can disrupt the host genome and potentially lead, to oncogenic effects. The use of RNA instead of DNA can effectively mitigate this potential risk. Specifically, RNA therapies do not integrate into the host genome, and their effects are transient, further minimizing

the risk of permanent genetic alterations. Therefore, compared to DNA therapies, RNA therapies are considered to have a significantly lower genotoxic risk, as RNA does not permanently remain in the cells and does not induce persistent changes in genetic material.

RNA Therapies in Kidney Disease

Currently, the drug market is primarily composed of two categories of drugs: small molecules and proteins.[38] However, these molecules have a limited range of disease targets for proteins or genes and cannot adequately address the required therapeutic needs.[39] Based on the characteristics of RNA drugs, RNA therapeutics can be divided into three categories. The first category includes oligonucleotide therapeutics, which interact with pre-mRNA, mRNA, or proteins to modulate gene expression in cells, including ASOs, siRNA, miRNA, RNA aptamers, etc. The second category comprises RNA drugs that are translated into proteins, such as in vitro transcribed mRNA. The third category involves therapeutic genome editing, where RNA serves as a guide for effector proteins that modify cellular DNA sequences (Figure 1). This chapter summarized the current research progress and clinical applications of RNA therapy in kidney diseases.

Oligonucleotide Therapy

Over the past few decades, oligonucleotide therapeutics (including ASOs, siRNA, miRNA, aptamers, and decoys) have emerged as increasingly important tools in nephrology and other fields.[40–42] These promising drugs leverage specific mechanisms for therapeutic effects. For instance, siRNA promotes mRNA degradation by attaching to specific sequences within the coding area, thereby increasing its promise as a therapeutic tool. ASOs identify and attach to complementary sequences of DNA or RNA, supporting proper mRNA splicing, averting faulty protein production, or directing RNA toward degradation. Furthermore, aptamers are sequences of oligonucleotides that form specific three-dimensional shapes, enabling them to interact with various targets (such as proteins, cells, microorganisms, compounds, and additional nucleic acids). Their binding to proteins can inhibit protein-protein interactions, yielding therapeutic effects (Figure 1). A significant benefit of focusing on the kidney is that oligonucleotide therapies are rapidly removed from the bloodstream via renal filtration, improving their distribution within the kidney compared to other organs.[43] This section presented the key strategies utilized in the creation of oligonucleotides-based therapies, as well as their recent progress in treating renal diseases, which are also detailed in Table 1.

ASO Therapeutics

ASOs are single-stranded RNAs that hybridize complementarily to messenger RNA (mRNA) encoding proteins, thereby inhibiting their translation into protein. ASOs utilize various mechanisms of action; however, approved drugs can be classified into two broad categories based on their mechanisms (Figure 1).

The initial category of ASOs promotes the cleavage of target mRNA by attaching to a specific sequence. Generally, these ASOs are modified to contain a DNA-based central sequence that is bordered by chemically altered RNA. When a duplex is formed with the target RNA, the central segment creates a DNA-RNA hybrid that is detected by RNase H. This enzyme then cleaves the RNA sequence within the duplex, resulting in the degradation of the target RNA. As this drug class relies on RNase H, which is active in both the nucleus and cytoplasm, they can efficiently target non-coding elements,[77] which is different from siRNA-based therapies that mainly operate within the cytoplasm. There are specific advantages in certain situations.[78] By now, some ASO medications for kidney disease have shown encouraging outcomes in clinical trials. The 2.5th generation APOL1 ASO (IONIS-APOL1 Rx) was selected as a clinical candidate because it has demonstrated its reliable and strong efficacy in studies using genomic *APOL1* transgenic mice. Subcutaneous administration of IONIS-APOL1 Rx into APOL1 G1 transgenic mice led to a reduction in APOL1 mRNA levels in the kidney and liver that was dependent on the dose, thereby effectively preventing interferon-induced proteinuria in a dose-dependent manner.[79] This drug has been utilized in a first-in-human single ascending dose Phase I study (NCT04269031) aimed at evaluating the safety and pharmacokinetics of a single ascending dose of subcutaneous ASO (ION532, also referred to as AZD2373), although the results have not yet been published. Additionally, another clinical study is currently ongoing (NCT05351047). A Phase 2 trial evaluating the efficacy of an ASO targeting apolipoprotein(a) in patients with hyperlipoproteinemia(a) and cardiovascular diseases has shown promising results (NCT03070782). This suggests that it may also be beneficial for

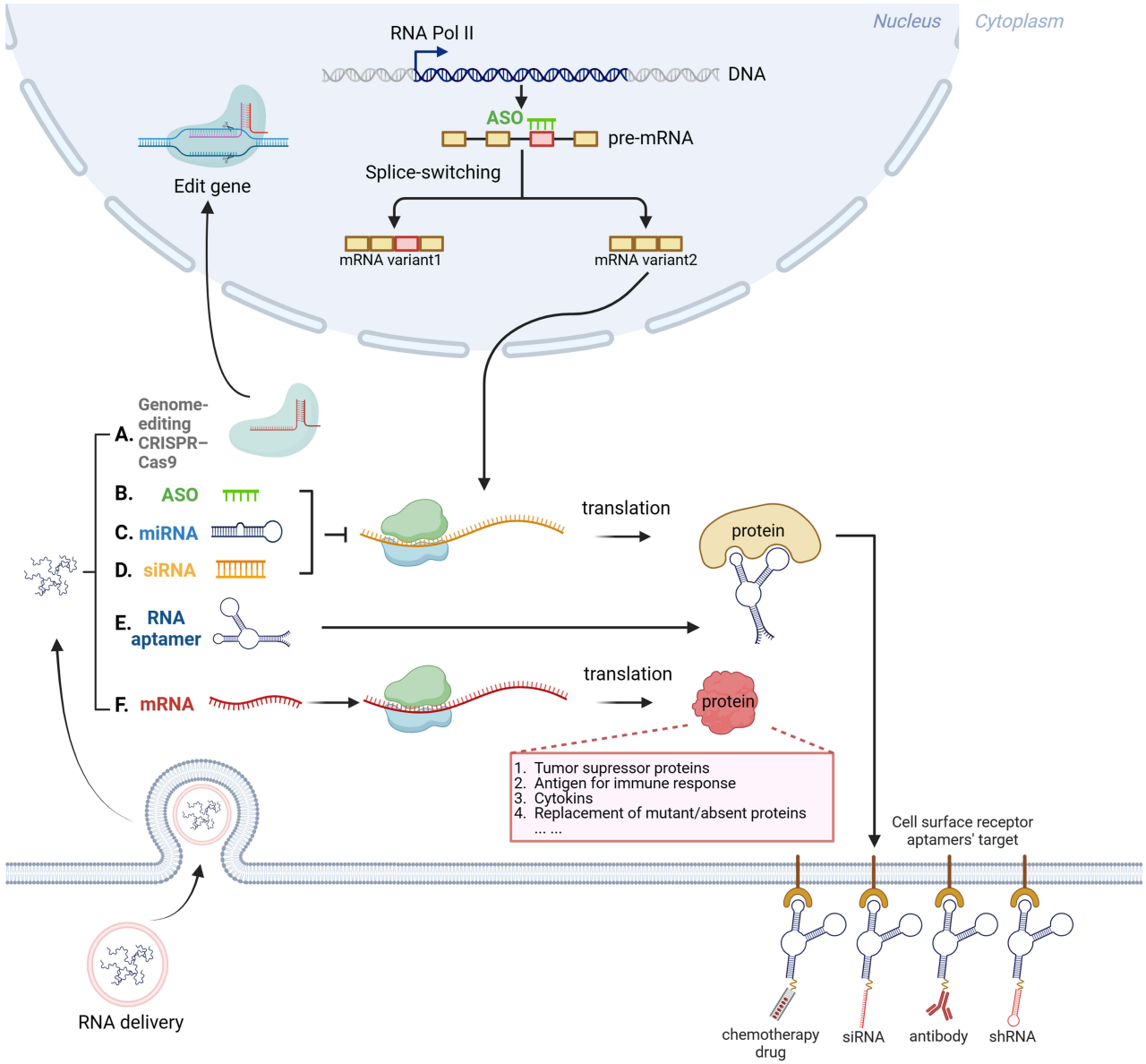

Figure 1 The mechanism of RNA therapies. RNA-based drugs can target various stages of protein coding and gene expression. For instance, mRNA encoding Cas9 has the potential to edit the genome. ASO can modulate splicing, while mature mRNA can be targeted by ASO, siRNA, or miRNA. The function of proteins can be regulated through the binding of aptamers. Additionally, exogenous mRNA can be utilized to introduce specific proteins into cells, either to supplement deficient enzymes or to serve as antigens, cytokines, and other molecules that can trigger immune responses.

treating kidney disease where lipoprotein(a) levels are implicated. Furthermore, the overproduction of complement factor B (CFB) has been linked to the exacerbation of IgA nephropathy. In response, Ionis partnering with Roche has developed IONIS-FB-LRx, a ligand-conjugated ASO therapeutic designed to target FB aimed at reducing IgA production and alleviating the symptoms associated with IgA nephropathy (NCT04014335, NCT05797610). Additionally, a current study has been evaluating an ASO aimed at the renal sodium-glucose cotransporter 2 to reduce blood glucose levels in individuals diagnosed with type 2 diabetes (NCT00836225).

Several ASO drugs have demonstrated therapeutic potential in animal and cell models. For instance, Guha et al have utilized an ASO-gapmer, which specifically inhibits the expression of connective tissue growth factor (*Ctgf*) in a mouse model of diabetic nephropathy, thus alleviating the associated symptoms.[47] Another study has employed an ASO-gapmer to silence *Kras* in a rat model of unilateral ureteral obstruction (UUO), significantly improving the pathological phenotype.[48] Additionally, several ASOs have shown promising therapeutic effects in mouse models of polycystic

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Table 1 The Research and Application of RNA Drugs in Kidney Diseases

RNA therapy	Model	Disease	Target	Sequence (5′-3′)	Reference
ASO	Mice	Kidney renal clear cell carcinoma	*NUDT21*	CGUGCGGGAAGCGGUUAUCUGCAAU	[44]
	Mice	Polycystic kidney disease	Enhanced *ASNS* expression	TATTTTATCACACTCC	[45]
	Mice	Renal cell carcinoma	*circehd2*	GCTGGTGCGAGCTACGACTT	[46]
	Clinical	IGA nephropathy	*CFB*	Not given	NCT04014335, NCT05797610
	Clinical	Kidney injury	*APOL1*	Not given	NCT03070782
	Clinical	Diabetic nephropathy	*Sodium-glucose cotransporter 2*	Not given	NCT00836225
	Mice	Diabetic nephropathy	*Ctgf*	CCACAAGCTGTCCAGTCTAA	[47]
	Rats	Diabetic nephropathy	*Kras*	Kras-1—ATTCACATGACTATACACCTKras-2—CACACTTATTCCCTACTAGG	[48]
	Xenograft model in mice	Renal cell carcinoma	*VEGF*	CTCACCCGTCCATGAGCCCG	[49]
	Mice	Polycystic kidney disease	*mTORC*	TCCACTTTTCACAGCACTGC	[50]
	Cell	Renal fibrosis	Block EDA exon inclusion	TCAATGTCTGTTAGG	[51]
	Mice	Cystic kidney	Exon 41 skipping	ATGTTTCTTCACATACCTTTTCTTT	[52]
siRNA	Mice and rats	Glomerulonephritis	*MAPK1*	UGCUGACUCCAAAGCUCUGdTdT	[53]
	Mice	Renal fibrosis	*Smad4*	GAUGAAUUGGAUUCUUUAATT	[16]
	Mice	Glomerulonephritis	*P38&p65*	*p38α*—GGUCACUGGAGGAAUUC*p65*—GCGACAAGGUGCAGAAAGA	[54]
	Mice	Lupus nephritis	*HMGB1*	Not given	[55]
	Mice	Renal inflammation	*P65*	CACCATCAAGATCAATGGCTA	[56]
	Mice	Diabetic nephropathy	*NLRP3*	Not given	[57]
	Mice	Diabetic nephropathy	*HDAC4*	GGUGCUUAUGGAAAGGGAUTT	[58]
	Clinical	Primary hyperoxaluria type 1	*HAO1*	Not given	NCT04152200
	Rats	Ischemia- or nephrotoxicity-related kidney injury	*P53*	GAAGAAAATTTCCGCAAAA	[59]
	Mice	Acute kidney injury	*miRNA-1β and p53*	Not given	[60]
	Mice	Acute kidney injury	*CD40*	GUGUGUUACGUGCAGUGACUU	[61]

miRNA	Clinical	Alport nephropathy	Anti-miR21	Not given	NCT02855268
	Mice	Diabetic nephropathy	Anti-miR192	GGCTGTCAATTCATAGGTCAG	[62]
	Mice	Acute kidney injury	miR204 mimics	UCCCGGUAAUCCCUUACCUGGUU CCCUUCCUU	[63]
	Mice	Acute kidney injury	miR211 mimics	UCCCGGCUUUCCCUUACCUGGUUUUCCCCCUU	[63]
	Mice	Acute kidney injury	Anti-miR107	Not given	[64]
	Clinical	AD polycystic kidney disease	Anti-miR17	Not given	NCT04536688
	Mice	Acute kidney injury	Anti-miR489	Not given	[65]
	Mice	Acute kidney injury	Anti-miR668	Not given	[66]
	Mice	Acute kidney injury	miR199a-3p mimics	Not given	[67]
	Mice, rats, pigs	Acute kidney injury	Anti-miR182-5p	Not given	[68]
ADDIN EN.CITE.DATA ADDIN EN.CITE aptamer	Mice	Diabetic nephropathy	RAGE	CCTGATATGGTGTCACCGCCGCCTTAGTATTGGTGTCTAC	[69]
	Mice	Diabetic nephropathy	Periostin	Not given	[70]
	Hypertensive mouse model	Glomerulonephritis	RAGE	CATTCTTAGATTTTTGTCTCACTTAGGTGTAGATGGTGAT	[71]
	Mice	Renal cell carcinoma	SW-4	ACTCATAGGGTTAGGGGCTGCTGGCCAGATATTCAGATGGTAGGGTTACTATGA	[72]
mRNA-based therapy	Clinical	Renal cell carcinoma	MUC1, CEA, Her2/neu, telomerase, survivin, and MAGE-A1	mRNA sequence	[73]
	Clinical	Renal cell carcinoma	Dendritic cells		NCT0067811
	Clinical	Renal cell carcinoma	IFN-α and IL-2		[74]
	Zebrafish	Cystine nephropathy	CTNS		[75]
	Mice	Methylmalonate nephropathy	Methylmalonate CoA mutase		[76]

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kidney disease (PKD) by targeting *mTORC1, mTORC2*, angiotensinogen, and asparagine synthase (*ASNS*), thereby regulating their mRNA expressions.[45,50,80] The potential of ASOs for targeted modulation of renal cell carcinoma (RCC) development and metastasis has also been explored in both in vitro and in vivo models. These ASOs can impede RCC progression by inhibiting the expression of tumor oncogenes such as vascular endothelial growth factor (*VEGF), Ki67*, and *circEHD2*.[44,46,49,81,82] Collectively, these studies underscore the significant potential of novel ASO-based therapeutic strategies for the treatment of kidney diseases.

The second category of ASO therapies mainly influences the pre-mRNA splicing process via a steric hindrance mechanism. Numerous RNA-binding proteins engage with specific sequences in pre-mRNA, which in turn regulates additional splicing factors, leading to diverse alternative splicing patterns.[83,84] Occasionally, these alternative splicing variations may play a role in disease onset. ASO drugs in this category can accurately target these sequences in pre-mRNA, thus impeding disease progression by modulating alternative splicing. This ability is distinctive to ASOs and offers new potential strategies for treating a range of genetic disorders. Multiple ASO therapies have been approved by the US Food and Drug Administration (FDA), such as nusinersen, eteplirsen, and golodirsen, aimed at modifying the splicing of target pre-mRNA. Regarding kidney diseases, studies have shown that exon skipping mediated by ASO can improve the ciliary structure and restore the placement of the CEP290 protein at the cilia's base in individuals with Joubert syndrome harboring nonsense mutations in *CEP290* exon 41. This strategy has also been confirmed through experiments using mouse models. The use of an ASO targeting technique can facilitate alternative splicing within intron 25 of the *CEP290* gene in mice, which in turn aids in partially rescuing the complete *CEP290* transcript and protein, ultimately enhancing renal ciliary length and alleviating cystic kidney disease symptoms.[52] Furthermore, another type of ASO has been shown to inhibit EDA exon inclusion, thereby reducing TGFβ-induced profibrotic effects and enhancing cell survival.[51] These findings indicate that ASO therapies hold significant potential for the treatment of alternative splicing-associated kidney diseases.

siRNA-Based Therapeutics

siRNAs are short double-stranded RNAs with typically 20–27 nucleotides in length, which specifically target and degrade mRNA in a sequence-dependent manner. siRNA technology has demonstrated considerable potential in the treatment of kidney diseases, not only helping to understand the molecular mechanisms underlying these conditions but also promoting various treatment strategies for kidney diseases.[85] A previous study has shown that modulation of *Mapk1* silencing can ameliorate glomerulosclerosis in a mouse model of glomerulonephritis,[53] while the use of siRNA targeting *Smad4* has been found effective in preventing renal fibrosis. These findings suggest that siRNA may serve as a pivotal therapeutic target for kidney disease.[16]

siRNA technology demonstrates significant therapeutic potential in certain kidney diseases. For example, the delivery of p38α MAPK and p65 siRNA to glomerular endothelial and mesangial cells in an IgA nephropathy mouse model via LNP carriers effectively alleviates proteinuria, inflammation, and excessive extracellular matrix deposition.[54] In lupus nephritis, co-delivery of siRNA targeting dihydroartemisinin and *HMGB1* produces a therapeutic effect by inhibiting the TLR4 signaling pathway.[55] In cases of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, siRNA targeting *p65* reduces endothelial cell NF-κB activation and mitigates renal inflammation.[56] In diabetic nephropathy, siRNA targeting *NLRP3* and *HDAC4* attenuates podocyte damage and renal lesion progression, respectively.[57,58] Primary hyperoxaluria type 1 (PH1) is a hereditary kidney disease characterized by excessive oxalate production, which can lead to kidney stones, renal failure, and widespread toxicity. The siRNA drug (Oxlumo) developed by Alnylam was approved by the FDA in 2020. It reduces urinary oxalate excretion in PH1 patients by targeting the *HAO1* gene.[86,87] Clinical studies have indicated that after Oxlumo treatment for 6 months, most patients have achieved oxalate levels close to normal (NCT04152200).

Additionally, siRNA technology has demonstrated significant efficacy in AKI. In cases of ischemia- or nephrotoxicity-related kidney injury, siRNA targeting *p53* has been shown to effectively protect proximal tubule cells and preserve kidney function.[59] Furthermore, siRNA targeting *meprin-1β* and *p53* has been effective in preventing kidney damage in a cisplatin-induced AKI model.[60] However, siRNA targeting *CD40* has been observed to reduce inflammation and promote kidney repair in a unilateral ureteral obstruction-induced AKI model.[61] Glevova et al[88] have assessed the

potential of 53 various siRNA targets, mainly related to apoptosis, inflammation, and immune rejection pathways after transplant-related ischemia-reperfusion. Although this approach remains under development, it has achieved promising results in mouse models.[89]

Notably, siRNA drug delivery systems are also being continuously optimized, including polycationic cyclodextrin nanoparticles and E-selectin-targeted liposomes. These delivery systems can enhance the specificity and efficiency of siRNA in the kidney.[90]

miRNA-Based Therapeutics

miRNA consists of single-stranded ncRNA with approximately 22 nucleotides in length, which binds to the 3′ untranslated region (UTR) of target mRNA through partial complementarity, primarily mediating translation inhibition and mRNA decay. miRNA-based therapeutic approaches include the use of anti-miRNA oligonucleotides (AMOs), miRNA antagonists, miRNA sponges, miRNA mimics, and target site blockers (TSB) to modulate miRNA function.[91,92]

miRNAs play a crucial role in the regulation of post-transcriptional gene expression, with their abnormal expression closely associated with various diseases, particularly kidney diseases (such as AKI,[93] kidney transplantation,[94] polycystic kidney disease,[95,96] and renal fibrosis.[97,98] As novel biomarkers and therapeutic targets, miRNAs can be detected in plasma and urine exosomes, demonstrating their potential for disease diagnosis and monitoring.[99,100] Moreover, as indicated by the results of animal models, the pathological processes of kidney disease can be ameliorated by regulating specific miRNAs, including anti-miR21, anti-miR192, miR204 mimics, miR211 mimics, and anti-miR107.[15,62–64,68,101] Furthermore, miRNAs have also shown promise in the treatment of ischemic kidney injury.[65–68]

Although miRNA-based therapy holds significant promise, its clinical translation encounters several challenges, including the need for a comprehensive understanding of the miRNA regulatory network associated with the disease, cell or organ-specific regulation, and potential off-target effects. Currently, there are 4 miRNA-based therapies in clinical development, two of which specifically target kidney disease:[93] the anti-miR21 drug RG012 [currently in phase 2 clinical trial for Alport nephropathy (NCT02855268)[101] and RGLS4326 [an antagonist that inhibits miR17 in autosomal dominant polycystic kidney disease (ADPKD), currently in Phase 1 clinical trial (NCT04536688)[102]. These findings offer hope for future evaluation of the clinical utility of miRNA mimics and inhibitors aimed at key pathological renal pathways.

RNA Aptamer Therapy

Aptamers are special DNA or RNA oligonucleotides that bind to various molecular targets with high affinity and specificity, including proteins, inorganic molecules, and complex biosystems.[103] They are selected through the SELEX method, involving multiple rounds of incubation and PCR amplification to identify the sequences with the strongest binding affinity and specificity.[104] Aptamers have been widely used in biomedical and non-medical areas, such as pesticide residue detection.[104] Their high target specificity offers a significant advantage in oligonucleotide-based therapies, addressing delivery problems and off-target effects.[105,106]

In renal diseases, aptamers have shown potential as diagnostic tools and targeted therapies. For example, aptamers selected by cell-SELEX specifically bind to pathophysiologically altered renal cells, demonstrating higher binding specificity compared to non-stimulated cells[105] This study suggested aptamers may be valuable for renal disease treatment. Additionally, aptamers have been developed to target specific receptors and modulate intracellular pathways, and their effectiveness in treating renal injury have been demonstrated.[69–71] Additionally, aptamers with high binding affinity and specificity to RCC cell lines have also been identified, which may be used in RCC identification and targeting[72] Wang et al[107] have employed cell-SELEX technology to develop the RCC nucleic acid aptamer probe W786-1 (Kd = (9.4 ± 2.0) nmol/L), with the RCC cell line 786-O as the target and 293T cells as the control. Following structural optimization, the short sequence W786-1S (48 nucleotides) was derived, retaining its ability to recognize 786-O cells and confirming that its target is a cell surface membrane protein. W786-1 exhibits strong binding affinity and selectivity at physiological temperatures, indicating its potential for RCC diagnosis and treatment. Additionally, Zhang et al[72] have identified the nucleic acid aptamer SW-4 (Kd ≈ (45.92 ± 5.58) nmol/L) from the Swan Library, which exhibits high affinity and specificity for 786-O cells while showing no binding to HEK293T or HK-2 cells. The optimized SW-4b is internalized by target cells, and fluorescence imaging reveals its robust recognition capability, along with

significant anti-proliferative activity against 786-O cells, effectively inhibiting the progression of the S phase of the cell cycle. SW-4b is a novel promising tool for RCC diagnosis and targeted therapy, and future studies involving tumor-bearing mice should be conducted to validate its tumor suppressive function.

However, limited studies have been reported on aptamers in renal diseases, and in vitro-SELEX-selected aptamers may have limitations when translated to in vivo organisms.[108] The in vivo-SELEX approaches using animal models of renal diseases could lead to the development of aptamers with enhanced therapeutic or targeting potential.

mRNA-based Therapeutics

With notable progress in mRNA-driven nanotechnology, groundbreaking therapies have been created for various illnesses, especially in the field of cancer treatment. mRNA-based therapies have shown significant potential in the realms of immunotherapy and vaccine development, and their potential applications are rapidly increasing. In this section, we outline the latest advancements in mRNA-based therapies that have been incorporated into preclinical and clinical studies aimed at combating kidney cancer. We provide an overview of the utilization of mRNA-encoding tumor antigens, cytokines, and tumor suppressors in the context of renal tumors.

Vaccines

Vaccines utilizing mRNA can be crafted according to the specific tumor antigens found in cancer cells, which subsequently elicit strong immune responses from both T cells and B cells against tumors in the body.[108,109] Tumor antigens are primarily divided into two categories: tumor-associated autoantigens (TAAs) and tumor-specific antigens (TSAs.[110] TAAs are generally found in high quantities in tumor cells, but they are also present in normal tissues, which leads to relatively limited tumor specificity and immunogenicity. Conversely, TSAs are neoantigens generated by mutations within tumor cells with greater tumor specificity and immunogenicity, although they tend to elicit lower tolerance in the organism.[111] Since the groundbreaking introduction and assessment of the first mRNA cancer vaccine,[112] extensive preclinical and clinical investigations have thoroughly demonstrated the potential of mRNA vaccines in the field of cancer therapy.

In tumor treatment, tumor-associated antigen (TAA) vaccines are among the most widely utilized. However, mammals typically exhibit high immune tolerance to individual TAAs. Therefore, the strategy of employing a combination of multiple TAAs is increasingly receiving attention, intending to enhance the therapeutic efficacy of cancer vaccines.[73] For instance, a phase I/II trial[73] involving 30 metastatic RCC patients has evaluated an mRNA-based vaccine formulation comprising a mixture of in vitro transcribed RNA encoding 6 distinct TAAs (including MUC1, CEA, Her2/neu, telomerase, survivin, and MAGE-A1). According to the survival analysis results, there is a significant correlation between patient survival and the immune response to the TAAs encoded by the naked mRNA vaccine, marking it as one of the pioneering vaccination studies in the realm of RCC.

Given the critical role of dendritic cells in inducing specific tumor antigen responses, they are an ideal and commonly utilized delivery vehicle for mRNA cancer vaccines. Dendritic cells primarily originate from the patient's own body and can effectively generate an mRNA vaccine after transfection with the corresponding mRNA. For instance, during the development of rocapuldencel-T (AGS-003), a single-arm, open-label Phase II trial has investigated the combined use of AGS-003 and sunitinib in 21 patients with intermediate- or high-risk RCC. The primary endpoint of this trial is the complete response rate, while secondary endpoints include overall survival (OS), progression-free survival (PFS), and safety. As indicated by the results, approximately 62% of patients achieved clinical benefit.[113]

While previous clinical trials have demonstrated some efficacy in the domain of mRNA cancer vaccines, the overall results are not optimal. To further enhance the efficacy, Xu et al have identified 4 potential RCC-specific neoantigen candidate genes through a comprehensive analysis of the TCGA-kidney renal clear cell carcinoma (KIRC) dataset: DNA topoisomerase II alpha (TOP2A), neutrophil cytoplasmic factor 4 (NCF4), formin-like protein 1 (FMNL1), and docking protein 3 (DOK3). These genes exhibit upregulation and mutation characteristics in KIRC and are closely associated with patient survival and the activity of antigen-presenting cells. This study not only validated TOP2A, NCF4, FMNL1, and DOK3 as potentially effective targets for the development of KIRC mRNA vaccines, but also aimed to further classify the immune subtypes of KIRC and identify RIS2, which may derive greater benefit from mRNA vaccination within the cancer patient population.[114]

Cytokine

Cytokines are soluble proteins primarily released by leukocytes. They form a complex superfamily of regulatory proteins that can finely modulate the activity of other immune system target cells.[115] Cytokines [such as interferons (IFNs) and interleukins (ILs)] are produced by eukaryotic cells in response to viral infections or various biological and synthetic inducers, exhibiting a wide range of biological and pharmacological properties.[115,116] Notable examples of clinically significant cytokines include ILs, IFNs (α, β, γ), colony-stimulating factors (such as G-CSF and GM-CSF), and tumor necrosis factor.

In the 1980s, IFN-α and IL-2 were extensively studied in phase II clinical trials for their anti-tumor activity against RCC.[74,117] In contrast, other cytokines (including IL-12, IL-6, IL-1, IFN-β, IFN-γ, and GM-CSF) did not demonstrate significant efficacy in subsequent phase II and Phase III clinical trials.[74,118–136] As a result, 7 phase II studies evaluating high-dose IL-2 therapy were approved by the FDA.[137] These studies continued to monitor patient toxicity and clinical outcomes and reported an overall response rate (ORR) of 15%, with 7% of patients achieving a complete response. Unfortunately, long-term disease control remains elusive for most patients.[138] Therefore, further research is essential to investigate the application of cytokines in kidney diseases, so as to better understand their efficacy and potential.

Encode for Disease-Related Proteins

Tumor suppressor genes are essential biological regulators that inhibit tumor development by preventing abnormal cell proliferation. However, they are frequently lost or functionally inactive in various tumors, thereby promoting tumor formation and progression.[139] Researchers have explored several strategies (including small molecule inhibitors, protein delivery technologies, and plasmid DNA-based gene transfection) to restore their function; however, these strategies still face significant limitations.[139] Recently, the use of mRNA nanoparticles encoding tumor suppressors for systemic delivery has emerged as a promising avenue. This is particularly important in RCC, where tumor suppressor genes (such as P53 and HIF1α) play critical roles in maintaining cellular homeostasis and inhibiting tumor growth.[140,141] Among them, the TP53 gene encodes the p53 protein (a major cancer preventive factor and has garnered particular attention regarding its function and regulatory mechanisms. Through self-assembly technology, TP53 mRNA can be efficiently encapsulated in nanoparticles, which significantly enhances stability and delivery efficiency, leading to high-level recovery of p53 protein and notable therapeutic effects in TP53 gene-deleted tumor models.[139] This discovery not only provides new experimental evidence for understanding the tumor suppression mechanism but also suggests that this strategy may be applicable for RCC treatment, although further research and validation are necessary to confirm this potential.

mRNA-based cytokine therapies aim to modulate the levels of cytokines in a targeted manner. Compared with traditional cytokine therapies that aim to either enhance or suppress specific cytokines, mRNA therapy introduces mRNA-encoding cytokines to enhance their production in a controlled manner, providing a novel approach. For example, mRNA vaccines encoding cytokines (such as IL-12) are being explored to boost immune responses. However, the immunogenicity of mRNA therapy involving stimulation of innate immune responses may pose challenges in terms of unwanted side effects, including activation of the inflammatory pathways. Therefore, the interplay between mRNA-induced cytokine production and the immune response remains a key consideration for optimizing the therapeutic applications of mRNA-based cytokine therapies in treating kidney diseases (such as kidney cancer and autoimmune kidney diseases).

Additionally, mRNA-based therapies are also being explored for conditions such as cystinosis and methylmalonic acidemia. These therapies aim to introduce mRNA into cells to produce the necessary proteins that are otherwise deficient due to genetic mutations; mRNA-based therapies offer the potential for treating these diseases by directly correcting the molecular deficiencies.[75,76]

Therapeutic Genome Editing

CRISPR and CRISPR–Cas9 systems comprise the Cas9 nuclease and single-stranded guide RNA (sgRNA), which are widely utilized as gene editing tools due to their speed, accuracy, and efficiency.[76,142] Compared with traditional therapies, CRISPR–Cas9 can circumvent the need for repeated administration and enhance therapeutic outcomes.[143] The successful delivery of both two components (Cas9 and sgRNA) to target cells is crucial for effective therapy.[144] The

delivery methods of Cas9 include protein, DNA, or mRNA forms.[144] Although direct delivery of Cas9 protein is relatively simple, it may induce adverse immune responses and encounter rapid degradation, resulting in a limited duration of gene editing efficacy.[145] Additionally, the considerable mass (160 kDa) of the Cas9 protein poses difficulties for delivery systems, whether viral or non-viral.[145] Common vectors for delivering Cas9 as DNA include plasmids and adeno-associated viruses (AAVs), which allow for prolonged expression of the protein but may result in increased off-target effects. AAVs exhibit low efficiency in editing tissues outside the liver and show high levels of hepatotoxicity, which increases the likelihood of off-target mutations occurring in non-cancerous cells.[145] Recently, the use of in vitro transcribed mRNA has surfaced as an alternative transient method for delivering Cas9, which can significantly minimize off-target impacts and genotoxic concerns, thereby enhancing gene editing efficacy.[146,147]

The CRISPR/Cas9 system holds significant promise for the treatment of kidney diseases,[40] as many such conditions (including autosomal dominant polycystic kidney disease and Alport syndrome) are caused by genetic mutations. Nevertheless, the application of gene editing in solid organs encounters challenges related to efficiently delivering the system to specific cells or tissues. Therefore, the use of this technology in kidney research is currently confined to the development of innovative in vitro models (utilizing human organoids) and in vivo models of kidney diseases. These models facilitate a deeper understanding of the molecular mechanisms underlying kidney disease and aid in the identification of novel disease progression-associated genes, as well as potential therapeutic targets.[148,149]

Another potential application of CRISPR/Cas9 technology is in the expansion of available sources for kidney transplants. Some researchers have proposed the possibility of cross-species organ transplantation, particularly using organs from pigs. However, this approach has resulted in severe immune responses in the human body, leading to rejection of donor organs. Nevertheless, CRISPR/Cas9 has emerged as a promising tool to address this challenge. Researchers have utilized CRISPR/Cas9 to genetically modify pig eggs, resulting in a lack of animal carbohydrate xenoantigens, which significantly reduces their recognition by human and non-human primate antibodies.[150] Additionally, modifications have been made to induce MHC-I deletions in pigs.[151] Higginbotham et al have demonstrated the feasibility of this method for the first time, achieving long-term transplantation success (over 125 days) from pigs to primates.[152]

Conclusions and Outlook

In recent years, the use of RNA-based approaches to treat kidney disease has gained significant importance, and several studies and drugs are currently in clinical development (Table 1). Although research has demonstrated that RNA-based therapies can effectively reach kidney cells and elicit therapeutic effects, targeted delivery within the body remains a significant challenge for the widespread application of these therapies. Currently, most ASO therapies utilize local delivery. However, when administered systemically, these drugs are frequently retained in various other organs, which may lead to off-target effects, side effects, and potentially renal toxicity. Additionally, the application of RNA technology still faces multiple challenges related to immunogenicity, stability, delivery efficiency, and intracellular effects.

These challenges, especially off-target effects and immunogenicity, remain significant barriers to the clinical use of RNA-based therapies. Although efforts are being made to improve RNA stability and reduce immune responses, addressing off-target effects is essential for the safe and effective use of these therapies. The use of RNA chemical modifications, advanced delivery systems, and kidney-specific ligands could enhance targeting precision and minimize unintended interactions with other organs, thereby reducing side effects. Further research into developing RNA delivery systems that minimize off-target effects and improve specificity is of great significance for the translation of RNA therapies from animal models to human patients.

When evaluating RNA therapies for specific renal diseases, various RNA-based approaches show promise depending on the disease's characteristics. For example, ASOs can effectively target specific genetic mutations in inherited kidney diseases, such as polycystic kidney disease. siRNA therapies are promising for conditions like diabetic nephropathy and AKI by silencing harmful genes or pathways. Additionally, ncRNAs, such as miRNAs, hold potential for addressing fibrosis and inflammation-related kidney diseases. Ongoing clinical trials are essential to confirm the clinical viability of these approaches and identify optimal strategies for their use.

Recent advancements in RNA delivery systems, including improved lipid nanoparticles and other targeted vehicles, have shown promise in overcoming some of these challenges. Innovations in ncRNA therapies, particularly miRNAs and

lncRNAs, could further improve the therapeutic outcomes of RNA-based treatments for kidney diseases. Clinical studies will help evaluate the practicality and clinical benefit of these innovations, guiding their integration into standard treatment protocols.

Thus, the potential applications of RNA-based therapies are vast. A deeper understanding of their specific roles in renal diseases will significantly contribute to advancing nephrology. Clinical evidence generated through these studies will be instrumental in establishing RNA therapies as a new treatment paradigm, with the potential to improve patient outcomes and reduce disease burden.

We have focused our discussion on RNA technologies and delivery strategies and have removed references to cytokine therapies to maintain the focus on RNA-based treatments for kidney diseases. Overall, this review emphasizes the critical role RNA-based therapies play in revolutionizing the treatment of kidney diseases, particularly with the continuous improvement of targeted delivery systems and specificity.

In summary, RNA technology not only accelerates the rapid development and production of mRNA vaccines but also introduces new research directions and treatment strategies in the field of nephrology. The continuous development of RNA-based therapies, alongside advances in delivery systems and targeting strategies that specifically address immunogenicity and off-target effects, may significantly enhance the treatment of kidney diseases. By assessing and tailoring RNA therapies to specific renal conditions, we can maximize their therapeutic potential and ultimately provide more effective and personalized treatments for kidney diseases. Integrating clinical trials with ongoing advancements in RNA technology will be key to fully realize the therapeutic potential of these treatments in clinical practice.

Author Contributions

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

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