

Circular RNA as emerging precision therapeutics: from RNA regulation to peptide translation

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Abstract

Circular RNAs (circRNAs) are a class of endogenous non-coding RNAs characterized by a covalently closed-loop structure. Although initially regarded as splicing byproducts, circRNAs are now recognized as essential regulators of gene and protein expression and play important roles in various human diseases. In recent years, growing evidence has indicated that a subset of circRNAs can be translated through cap-independent mechanisms to produce bioactive peptides or proteins. These findings expand the functional scope of circRNAs and offer new opportunities for RNA therapy. This review summarizes recent advances in circRNA biology, with an emphasis on their potential in diagnosis and treatment. We also review the therapeutic strategies targeting circRNAs at both the RNA and protein levels and the delivery systems that support circRNA-directed therapies. After we discuss how circRNA therapeutics may be integrated into precision medicine, we further highlight the current clinical progress and key challenges for advancing circRNA-based therapies toward clinical application.

Keywords: circular RNA, circRNA, RNA biology, oncogenesis, therapy

Introduction

Circular RNAs (circRNAs) are RNA molecules with covalently closed transcripts lacking 5' caps and 3' poly(A) tails that are generated by the back-splicing of precursor mRNAs [1, 2]. Early observations considered circRNAs as byproducts of RNA processing; however, subsequent studies have revealed that some circRNAs are abundant and conserved with diverse molecular functions [3–5]. Their circular structure leads to resistance to exonuclease-mediated degradation and remarkable molecular stability compared to mRNAs. This feature facilitates circRNAs to accumulate to high levels within cells and in extracellular spaces such as plasma and exosomes [6, 7]. In addition, circRNA expression is cell-, tissue-, and disease-specific, which indicates their biogenesis and biological functions are tightly regulated [8–10]. Consistent with this diversity, circRNAs participate in a range of biological processes, including transcriptional modulation via binding with transcription factors, post-transcriptional regulation through interactions with microRNAs and RNA-binding proteins (RBPs), and protein translation [11–13]. CircRNAs were traditionally classified as non-coding RNAs due to their inability to engage in canonical cap-dependent translation. Recent studies, however, challenge the view by showing that certain circRNAs can be translated via cap-independent mechanisms [14–16]. Considering these distinct characteristics, circRNAs are now acknowledged as dynamic regulators of cel-

lular homeostasis and disease pathogenesis with great potential to serve as diagnostic biomarkers and therapeutic targets [17, 18].

Precision medicine aims to tailor treatment decisions using biological markers, and it has traditionally focused on genomic alterations and protein-based indicators. However, these markers often fail to capture the ongoing regulatory changes that influence the disease progression and therapeutic response [19, 20]. Because of this limitation, the focus of precision medicine has shifted toward RNA-level regulation, which provides a more immediate and context-sensitive layer of biological information [21, 22]. Within this setting, circRNAs stand out due to their highly specific expression patterns and exceptional molecular stability, which allow reliable detection in tissues and biofluids and support their use as precise biomarkers [5, 6, 8]. In addition to the diagnostic applications, circRNAs can also be selectively targeted at their back-splice junctions (BSJs), avoiding the possible effects on their cognate linear transcripts during precise modulation [23]. The discovery of the translational potential of circRNAs broadens their biomedical significance and introduces an additional layer of functional and therapeutic interest for circRNAs [14–16].

In this review, we focus on circRNAs as useful regulators and therapeutic candidates in precision medicine, and summarize current knowledge on their biological functions, translational capacity, targeting approaches, and clinical potential

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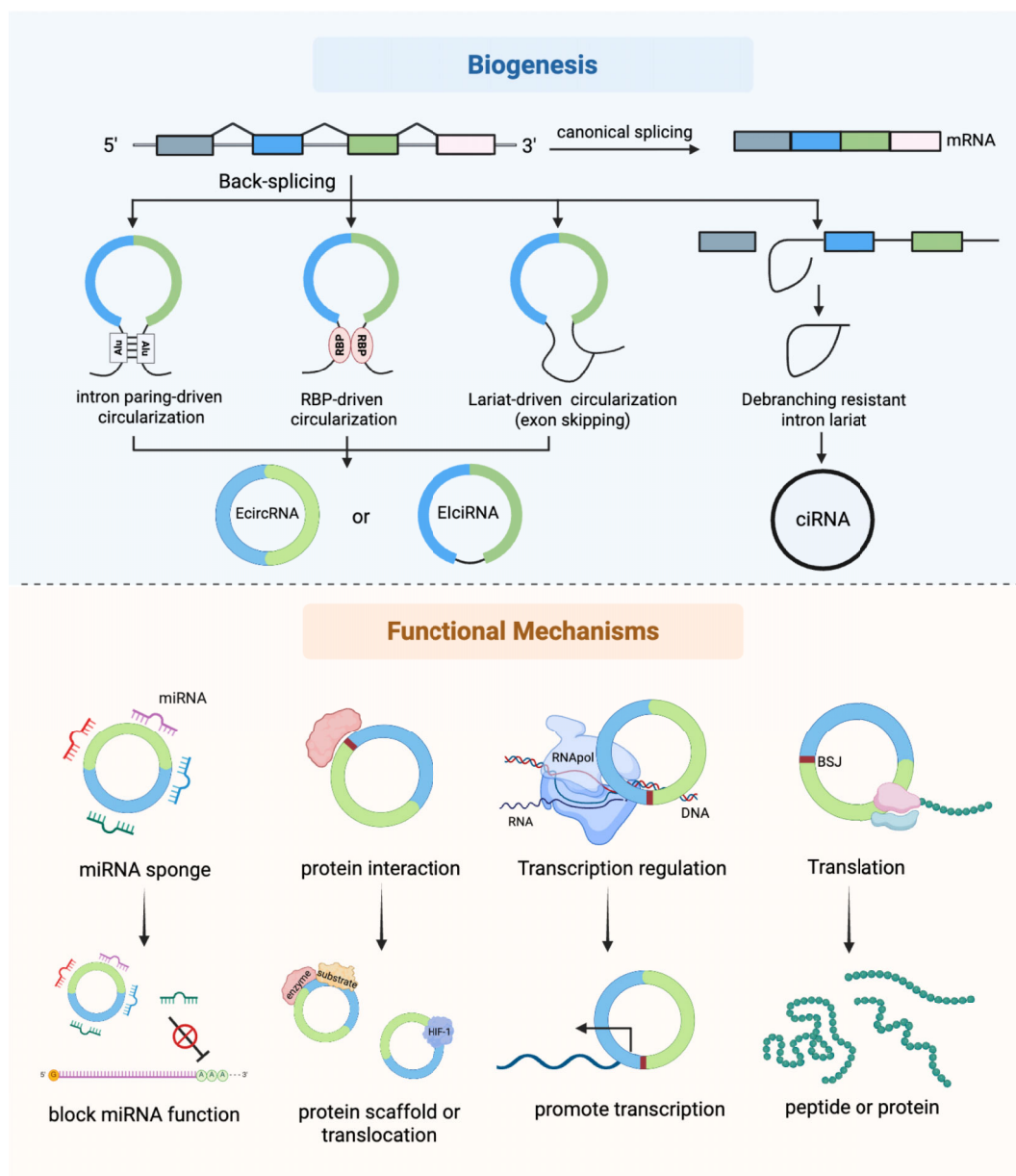


Figure 1 CircRNA biogenesis and major functional mechanisms. CircRNAs are generated from precursor mRNAs through back-splicing, mainly via intron pairing-driven, RBP-driven, or lariat-driven circularization. These pathways give rise to different circRNA species. After formation, circRNAs can act as microRNA sponges, bind RBPs, regulate transcription, or serve as templates for cap-independent translation. Created in BioRender. Wu, N. (2026). BioRender.com/d2kfw1

to support the development of circRNA-guided diagnosis and therapy.

CircRNAs in human disease

Biogenesis and functional mechanism of circRNAs

CircRNAs are generated mainly by back-splicing of precursor mRNAs. Three major biogenesis models are commonly described (Fig. 1): intron pairing-driven circularization, in which complementary sequences in flanking introns bring splice sites together [23]; RBP-mediated circularization, in which RBPs bridge nearby in-

trons to promote back-splicing [24]; and lariat-driven circularization, in which exon skipping first generates a lariat intermediate that is then processed into a circRNA [25]. These pathways give rise to different circRNA classes, including exonic circRNAs (ecircRNAs), exon-intron circRNAs (ElciRNAs), and circular intronic RNAs (ciRNAs). ciRNAs arise from intron lariats that escape debranching, whereas ElciRNAs retain intronic sequences after circularization and can regulate transcription in the nucleus [26, 27].

CircRNAs exhibit remarkable functional diversity, operating at multiple regulatory levels to control gene expression and cellular behavior (Fig. 1). Although the majority of circRNAs predominantly localize to the cytoplasm, a distinct subset resides in the nucleus where they participate in transcriptional regulation. Nuclear circRNAs can interact with transcription factors,

RNA polymerase II (Pol II), or chromatin-associated proteins to influence the transcription of their parental genes or other genomic loci. For example, intronic circRNAs (ciRNAs) associate with the Pol II transcriptional machinery to form functional complexes that enhance Pol II-mediated transcription [26]. Similarly, exon–intron circRNAs (EciRNAs) interact with U1 snRNA through specific RNA–RNA interactions, thereby promoting transcription of their parental genes [27]. The nuclear exonic circRNA FECR1 (FLI1 circular RNA) directly binds to the FLI1 promoter to activate gene transcription in breast cancer cells [28]. Beyond the nucleus, certain cytoplasmic circRNAs also indirectly regulate transcriptional programs. For instance, circAmotl1 forms a complex with the transcription factor c-Myc, facilitating its nuclear translocation and enhancing transcription of c-Myc downstream target genes [29].

At the post-transcriptional level, circRNAs are best known for their ability to act as molecular sponges or decoys. Thousands of circRNAs have been reported to harbor multiple microRNA-binding sites, allowing them to sequester specific microRNAs. By limiting microRNA availability, these circRNAs can relieve microRNA-mediated repression of target mRNAs, ultimately resulting in increased expression of downstream proteins [1, 11]. Besides acting as microRNA sponges, circRNAs can bind and sequester RBPs, modulating RBP subcellular localization or activity [13, 30]. Through these interactions, circRNAs influence mRNA splicing [31], stability [32], and translation [33]. However, this may not be the general function for most circRNAs, since many circRNAs possess few effective microRNA-binding sites.

Alongside with their regulatory roles at the RNA level, a subset of circRNAs has been shown to possess protein-coding potential via non-canonical mechanisms. Despite lacking a 5' cap and poly(A) tail, circRNAs can undergo cap-independent translation through internal ribosome entry sites (IRESs) or N⁶-methyladenosine (m⁶A)-mediated initiation, driving the recruitment of the translational machinery [15, 16, 34]. Ribosome profiling, polysome association, and mass spectrometry analyses have provided direct evidence that selected circRNAs are actively translated into peptides or proteins under specific cellular conditions. The updated prediction for translation of circRNAs increases the number of endogenously translatable circRNAs to >300 000 in the recent transCirc database [35]. Especially, circRNA translation is often tightly regulated by cellular state, stress conditions, and RNA modifications, and typically occurs at lower efficiency than linear mRNAs [36, 37]. Emerging studies indicate that circRNA-derived peptides can exert distinct biological functions, including regulation of signaling pathways, protein–protein interactions, subcellular localization of partner proteins, cellular stress responses, and disease-associated phenotypes. These findings support the view of circRNA translation as an additional, functionally relevant layer of circRNA biology [38–41]. The expanding translational potential of circRNAs is discussed in detail in the “Translational Potential of circRNAs” section.

Notably, circRNA functions are highly cell type-, tissue-, and stage-specific. A single circRNA may exert distinct roles depending on cell type, different tissue or organ, developmental stage, or disease state, arising from differences in interacting proteins or subcellular localization [10]. This multifunctionality illustrates the complexity of circRNA biology and strengthens the need to consider specific cellular contexts when evaluating circRNAs as biomarkers or therapeutic targets in precision medicine.

CircRNAs in pathophysiology

Accumulating evidence implicates circRNAs as important regulators of disease pathophysiology across different organs, with particularly well-established roles in cancer, cardiovascular disease, and neurodegeneration. In cancer, circRNAs can function as either oncogenic drivers or tumor suppressors, depending on their cellular state and molecular interactions [17, 42]. Oncogenic circRNAs have been shown to promote tumor cell proliferation, invasion, metastasis, and resistance to chemotherapy or targeted therapies, often through the regulation of oncogenic signaling pathways or interactions with microRNAs or RBPs [29, 43–45]. For example, the circRNA BISC was recently shown to mediate acquired resistance to BET inhibitors in triple-negative breast cancer by regulating IGF2BP2-dependent c-MYC translation [46]. Conversely, tumor-suppressive circRNAs can restrain malignant phenotypes by inhibiting cell cycle progression, inducing apoptosis, decreasing cell survival, or suppressing metastasis, highlighting the context-dependent nature of circRNA function in cancer biology [13, 47, 48]. Representative circRNAs implicated in cancer and their reported functions are summarized in Table 1.

In cardiovascular diseases, circRNAs have emerged as key regulators of cardiac injury and remodeling [49–51]. Dysregulated circRNA expression has been reported in myocardial infarction [52], cardiac hypertrophy [40], heart failure [53], fibrosis [54], and cardiomyopathies [55], where circRNAs influence cardiomyocyte survival [56], fibroblast activation [57], inflammation [58], and lipid or glucose metabolism [59]. Importantly, circRNA stability facilitates their detection in circulation, and multiple circulating circRNAs have been proposed as prognostic or predictive biomarkers for cardiac injury and disease progression.

The central nervous system is particularly enriched in circRNAs, with age-dependent and region-specific expression patterns [8]. In neurodegenerative diseases, brain-enriched circRNAs have been implicated in synaptic function [60], neuronal plasticity [61], and neuroinflammatory responses [62], processes that are critically disrupted during aging and neurodegeneration. Dysregulation of circRNA expression has been associated with Alzheimer's disease, Parkinson's disease, ischemic brain injury, and neuropsychiatric disorders, suggesting that circRNAs contribute to neuronal vulnerability and disease progression [63–67].

Clinical biomarker potential

The intrinsic molecular properties of circRNAs have placed them as promising clinical biomarkers for disease diagnosis and prognosis. Their covalently closed structure confers resistance to exonuclease-mediated degradation, resulting in superior stability compared with linear RNAs in tissues and biofluids. CircRNAs are readily detectable in plasma and extracellular vesicles (EVs) such as exosomes, supporting their application in liquid biopsy-based diagnostics [7, 68, 69]. Moreover, circRNA expression patterns are often highly tissue- and disease-specific, which is a key advantage for precision biomarker development. Representative circRNAs with validated or promising roles as diagnostic, prognostic, or predictive biomarkers are summarized in Table 2.

In oncology, multiple circRNAs have been associated with tumor progression and patient outcome [9]. For example, circ-AURKA and circ-AMACR were identified as potential diagnostic

Table 1 Representative circRNAs implicated in cancer and their reported functions.

circRNA	Cancer types	Expression pattern	Molecular mechanism	Functional consequence	Ref.
circACVR2A	Hepatocellular carcinoma	Upregulated	miRNA sponge	Promote the proliferation, migration, and invasion	[163]
circPVT1	Triple negative breast cancer	Upregulated	miRNA sponge	Increase tumorigenicity	[164]
circIGF2BP3	Non-small-cell lung carcinoma	Upregulated	miRNA sponge	Facilitate tumor immune evasion	[165]
circTRPS1	Bladder cancer	Upregulated	miRNA sponge	Modulate tumor microenvironments	[166]
circRNA-BISC	Breast cancer	Upregulated	Protein binding	Overcome BETi resistance	[46]
circITGB6	Colorectal cancer	Upregulated	Protein binding	Promote tumor metastasis	[43]
circ-hnRNP	Gastric cancer	Downregulated	Protein binding	Suppress tumorigenesis	[167]
circACTN4	Breast cancer	Upregulated	Protein binding	Facilitate the growth, invasion, and metastasis	[168]
circDNMT1	Breast cancer	Upregulated	Protein binding	Activate autophagy	[169]
circAMOTL1	Breast cancer	Upregulated	Protein binding	Promote tumorigenesis	[29]
circMAN1A2 (2,3,4,5)	Colorectal cancer	Upregulated	mRNA interaction	Cell proliferation and tumor progression	[170]
circSCRIB	Breast cancer	Upregulated	mRNA stability	Promote migration, invasion, and tumorigenesis	[171]
cFAM210A	Hepatocellular carcinoma	Downregulated	Protein binding, transcription suppression	Reduce proliferation, stemness, and tumorigenicity	[172]
circRMST	Neuroendocrine prostate cancer and small cell lung cancer	Upregulated	Protein recruitment, transcription activation	Promote tumor growth	[173]
circACTN4	Intrahepatic cholangiocarcinoma	Upregulated	miRNA sponge, protein recruitment, transcription activation	Promote proliferation and metastasis	[174]
circIPO11	Hepatocellular carcinoma	Upregulated	miRNA sponge, protein recruitment, transcription activation	Drive the self-renewal and promote the propagation	[91]
circINSIG1	Colorectal cancer	Upregulated	Encoding protein	Promote proliferation and metastasis	[175]
circMRPS35	Hepatocellular carcinoma	Upregulated	Encoding protein	Promote cisplatin resistance	[176]
circASK1	Lung adenocarcinoma	Downregulated	Encoding protein	Increase sensitivity to gefitinib	[177]
circEIF6	Triple-negative breast cancer	Upregulated	Encoding protein	Promote the proliferation and metastasis	[178]
circHNRNP	Multiple myeloma	Upregulated	Encoding protein	Promote MM progression	[179]

biomarkers for prostate cancer biomarkers, which can be detected in urine samples of prostate cancer patients [9]. Elevation of plasma hsa_circ_0000190 was reported to be correlated with poor response to immunotherapy and can be used to predict the survival outcomes of lung cancer patients [70]. Serum circAHS1

was correlated with lymph node metastasis and TNM stage in gastric cancer patients, indicating circAHS1 is a promising GC-specific biomarker for both diagnostics and target therapy [71]. These studies illustrate how circRNA expression profiles derived from tumor tissue or circulation may complement or, in some set-

Table 2 CircRNAs with validated or promising roles as biomarkers.

circRNA	Disease	Sample source	Biomarker type	Ref.
F-circEA (EML4–ALK fusion)	EML4–ALK + Non-small cell lung cancer	Plasma	Diagnostic	[180]
circMBOAT2, circDNAJC6, circTMEM56	Hypertrophic obstructive cardiomyopathy	Serum	Diagnostic	[69]
circPTPN22	Rheumatoid arthritis	PBMC (blood)	Diagnostic	[181]
hsa_circRNA_0039480	Gestational diabetes mellitus	Plasma	Diagnostic	[182]
circGAPVD1 (hsa_circ_0003270)	Colorectal cancer	Plasma exosome	Diagnostic	[183]
hsa_circ_0020840 and hsa_circ_0116108	Bacterial CNS infection	Plasma exosome	Diagnostic	[184]
hsa_circRNA_100632	Type 1 diabetes	PBMC (blood)	Diagnostic	[185]
8 circRNAs, e.g. hsa_circ_0045602, hsa_circ_0008768, hsa_circ_0007380	Gastric cancers	Serum	Diagnostic	[186]
circPRMT5	Bladder cancer	Serum and urine exosomes	Diagnostic/prognostic	[187]
circAHS1	Gastric cancer	Serum	Diagnostic/prognostic	[71]
hsa_circ_0000367, hsa_circ_0021647, hsa_circ_0000288	Cholangiocarcinoma combined with biliary obstruction	Bile and serum exosomes	Diagnostic/prognostic	[188]
circ-YOD1	Coronary artery disease	Blood	Prognostic	[189]
MICRA	Acute myocardial infarction	Whole blood	Prognostic (LV dysfunction)	[190]
hsa_circ_0058493	Chronic myeloid leukemia	PBMC, exosomes	Prognostic/predictive	[191]
hsa_circ_0000190	Lung cancer	Plasma	Predictive/prognostic	[70]
circTMTC3 and circFAM117B	Immunotherapy of melanoma	Tumor tissue	Predictive	[192]
CDR1as	SSRI antidepressants for major depressive disorder	Whole blood	Predictive	[193]
11 circRNAs, e.g. circMCCC2, circGPATCH2L, circATP9B	Immunotherapy of advanced non-small cell lung cancer	Tumor tissue	Predictive	[194]

tings, provide added value beyond conventional protein-based biomarkers.

CircRNAs have also emerged as clinically relevant biomarkers in cardiovascular disease, where early diagnosis and prognostic assessment remain major challenges. In patients with myocardial infarction, circRNA MICRA has been shown to predict left ventricular dysfunction and adverse remodeling following acute coronary events, providing prognostic information beyond currently established markers [72]. In addition, Sonnenschein *et al.* examined 64 patients with hypertrophic cardiomyopathy and 53 healthy controls and identified that the circulating circRNAs DNAJC6, TMEM56, and MBOAT2 can serve as potential biomarkers for hypertrophic cardiomyopathy. The serum levels of circTMEM56 and circDNAJC6 are correlated with disease severity [69]. The stability of circRNAs in circulation and their association with clinical outcomes support their use in cardiovascular risk stratification.

Encouragingly, the successful clinical translation of non-coding RNA biomarkers demonstrates that their diagnostic value is no

longer theoretical. Although circRNA-based biomarkers are not yet routinely used in clinical practice, the FDA approval of the PCA3 lncRNA urine test for prostate cancer provides clear evidence that non-coding RNAs can satisfy the regulatory requirements and deliver useful information [73, 74] (FDA Premarket Approval number: P100033). This example establishes a clear translational pathway for circRNAs, especially given their strong stability and reliable detection in biofluids. Consistent with this view, retrospective studies indicate that circRNAs can match, and in some cohorts outperform, commonly used protein biomarkers in diagnostic and prognostic settings [71, 75].

Despite these advantages, circRNA applications are still limited to preclinical research and clinical trials at present. Several challenges remain, including the absence of standardized methods for circRNA measurement, variability in RNA extraction and normalization, limited understanding of factors affecting circRNA stability, and the need for large, prospective multicenter studies to support regulatory approval. As these challenges are addressed, and drawing on regulatory experience from lncRNA- and microRNA-

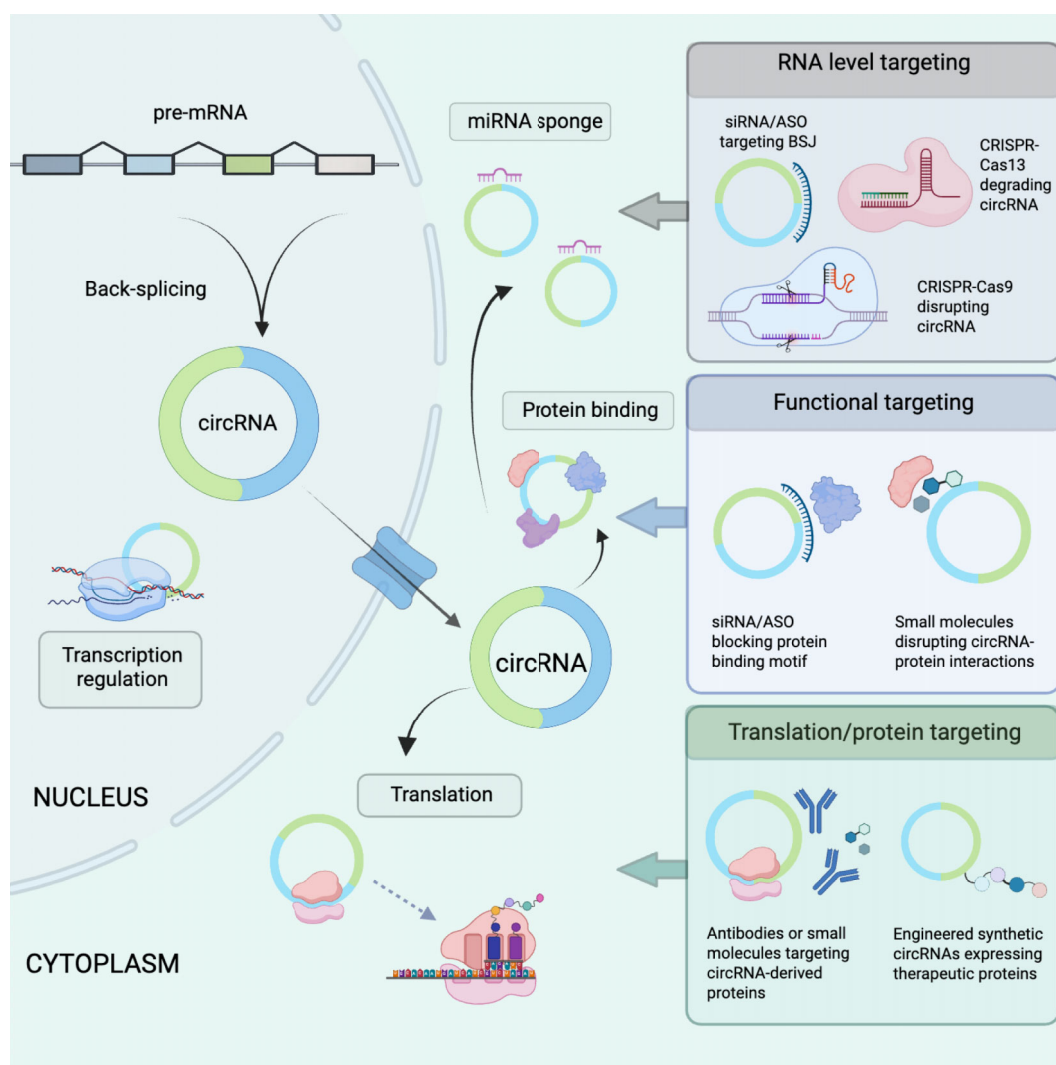


Figure 2 Functional roles of circRNAs and therapeutic modalities. circRNAs are generated through back-splicing of precursor mRNAs and localize in both the nucleus and cytoplasm. Nuclear circRNAs can regulate transcription, while cytoplasmic circRNAs participate in post-transcriptional regulation by sponging microRNAs or interacting with RBPs. A subset of circRNAs can be translated to functional peptides or proteins through cap-independent mechanisms. These diverse activities create multiple opportunities for therapeutic intervention. Direct strategies include RNA-targeting approaches such as siRNA, antisense oligonucleotides, and CRISPR-based methods. Indirect approaches aim to disrupt circRNA–protein interactions, inhibit circRNA-derived peptides, or use engineered synthetic circRNAs as therapeutic agents. Created in BioRender. Wu, N. (2026). BioRender.com/frp1rk7

based diagnostics, circRNAs are well placed to become clinically useful RNA biomarkers in precision medicine.

cRNA expression or function, as well as approaches that use circRNA-derived peptides and proteins for precision intervention (Fig. 2).

Therapeutic modalities targeting circRNAs

The expanding recognition of circRNAs as regulators of disease pathogenesis and clinically informative biomarkers has naturally prompted interest in their therapeutic targeting. Unlike conventional targets, circRNAs offer unique opportunities for intervention owing to their covalently closed structure and defined BSJs. These features support selective alteration of circRNAs at the RNA level or through interference with their downstream regulatory and translational outputs. In this section, we summarize current and emerging therapeutic modalities targeting circRNAs, with an emphasis on strategies that directly regulate cir-

Direct modulation of circRNA expression

Oligonucleotide- and CRISPR-based approaches

The siRNAs targeting BSJs were among the earliest approaches used to achieve circRNA knockdown. Studies targeting circRNAs such as circZNF609 and circHIPK3 demonstrated that siRNA-mediated silencing can reduce circRNA expression, although knockdown efficiency varies depending on siRNA sequence design and cellular condition [76–78]. These approaches have also been associated with unintended effects on cognate linear transcripts, highlighting the intrinsic limitations of siRNA-based strategies for selective circRNA targeting. Mechanistically, canonical siRNA activity relies on endonucleolytic cleavage of linear RNA substrates,

which compromises efficiency and specificity when applied to covalently closed circRNAs.

Antisense oligonucleotides (ASOs) offer another well-established way to directly target circRNAs by binding to their unique BSJs. This junction specificity allows selective regulation of circRNAs without disturbing the cognate linear mRNA expression [79]. Junction-targeting ASOs have been successfully applied to disease-relevant circRNAs, including circHIPK3 and circFOXK2 in cancer models, demonstrating efficient and selective circRNA suppression [80, 81]. Recent work using circular ASOs targeting circSlc8a1 demonstrated efficient and highly specific circRNA inhibition with minimal impact on the cognate linear SLC8A1 transcript, thereby overcoming a major limitation of siRNA-based approaches [82]. Moreover, an enzymatic ligation-based platform for synthesizing circular ASOs demonstrated robust, sequence-specific circRNA knockdown. This approach also addressed key drawbacks of linear ASOs, including reduced stability and limited durability [83]. Collectively, these studies highlight how structural compatibility between circular ASOs and circRNA targets can enhance both the selectivity and persistence of circRNA-directed modulation.

CRISPR-based strategies provide complementary tools for regulating circRNA at both the RNA and DNA levels. RNA-targeting CRISPR–Cas13 systems offer a programmable approach for selective degradation of cytoplasmic circRNAs and have been applied to selectively suppress circRNAs in cell models as well as in pooled, large-scale circRNA screening platforms. These approaches provide precise targeting without introducing permanent genomic modification. Several studies have demonstrated that CRISPR–Cas13 effectors can achieve more robust circRNA knockdown and reduce RNAi-associated off-target effects compared to siRNA-based approaches [84–86]. However, this strategy also has inherent limitations, including the requirement for accessible BSJ regions and guide sequences that may partially overlap with linear cognate transcripts, potentially constraining target selection [86–89]. At the genomic level, CRISPR–Cas9-mediated deletion of intronic complementary sequences required for back-splicing has been used to disrupt circRNA biogenesis, as demonstrated for circCSNK1G3 and circIpo11, while largely preserving linear transcript expression [90, 91]. Despite its effectiveness, the permanent nature of genome editing raises additional safety and ethical considerations, particularly for therapeutic applications.

Translational status and emerging circRNA therapeutic candidates

Despite rapid advances in circRNA biology and therapeutic engineering, circRNA-based interventions remain at an early stage of clinical translation. Most circRNA-targeting strategies are currently limited to preclinical studies, owing to both the relative novelty of circRNAs as therapeutic targets and the additional challenges associated with modulating circRNA species *in vivo*. Recent advances, however, have provided initial proof-of-concept evidence for circRNA therapeutics and have begun to outline plausible routes toward clinical translation. RXRG001, a lipid nanoparticle (LNP)-formulated circRNA designed to express human aquaporin-1 (AQP1) for the treatment of radiation-induced xerostomia, has entered Phase I/IIa clinical evaluation following regulatory clearance (ClinicalTrials.gov number: NCT06714253). This study repre-

sents the first registered evaluation of circRNA-based therapy in humans and demonstrates the feasibility of delivering and assessing synthetic circRNAs in a clinical setting. It also provides early regulatory and developmental insight for circRNA therapeutics, particularly those that rely on the stability and translational potential of circRNAs.

At this stage, several barriers must be addressed before circRNA targeting strategies can be translated more broadly. For CRISPR–Cas13-based approaches in particular, challenges related to delivery efficiency, immune response, and clinical scalability will need to be carefully addressed [92, 93]. More generally, the successful clinical translation will require tissue-specific delivery systems, precise control of circRNA expression or knockdown levels, comprehensive assessment of long-term safety, and the establishment of standardized manufacturing and quality-control pipelines [94–96]. Regulatory procedures for circRNA-based therapeutics are under development and will likely be informed by prior experience gained from mRNA- and RNAi-based therapies. Together, these considerations place circRNA-targeting strategies at an early but promising stage of therapeutic development. While clinical translation remains at an initial phase, continued methodological refinement and systematic evaluation are expected to support the transition from preclinical studies toward broader clinical testing.

Indirect strategies targeting circRNA-derived peptides and proteins

The finding that some circRNAs can be translated through cap-independent mechanisms adds a new therapeutic dimension beyond regulating RNA levels or RNA–protein interactions. In certain diseases, peptides or proteins produced from circRNAs have independent biological functions and directly contribute to pathogenic signaling. Targeting these translational products, rather than the circRNA itself, therefore represents a distinct and potentially more precise therapeutic approach [14, 15, 97].

As illustrated in Fig. 3, circRNA-directed therapies can act at two distinct levels to block circRNA-derived peptides: interference with translation initiation and direct targeting of the peptide or protein product. When circRNA expression does not closely match functional output, directly inhibiting the peptide or protein may be the more effective strategy. This approach is especially relevant when circRNAs also carry important regulatory functions unrelated to translation, or when peptide expression is limited to specific disease states or cell types [37, 98]. By separating RNA levels from protein activity, protein-level targeting allows more precise intervention while reducing disruption of broader circRNA-related regulatory networks. The therapeutic relevance of this approach is supported by growing evidence that circRNA-derived proteins can have direct disease-related functions. For example, a peptide encoded by circCDYL has been shown to exacerbate cardiac hypertrophy, while a protein translated from circFBXW7 suppresses glioma tumorigenesis [99, 100]. These findings indicate that circRNA-derived translation products can act as functional disease mediators and represent tractable therapeutic targets. Several intervention strategies may be applied at the peptide or protein level. Conventional protein-targeting approaches, such as small-molecule inhibitors, neutralizing antibodies, and peptide antagonists, may be adapted once the structure and function of these products are defined [101, 102]. Moreover, translation-

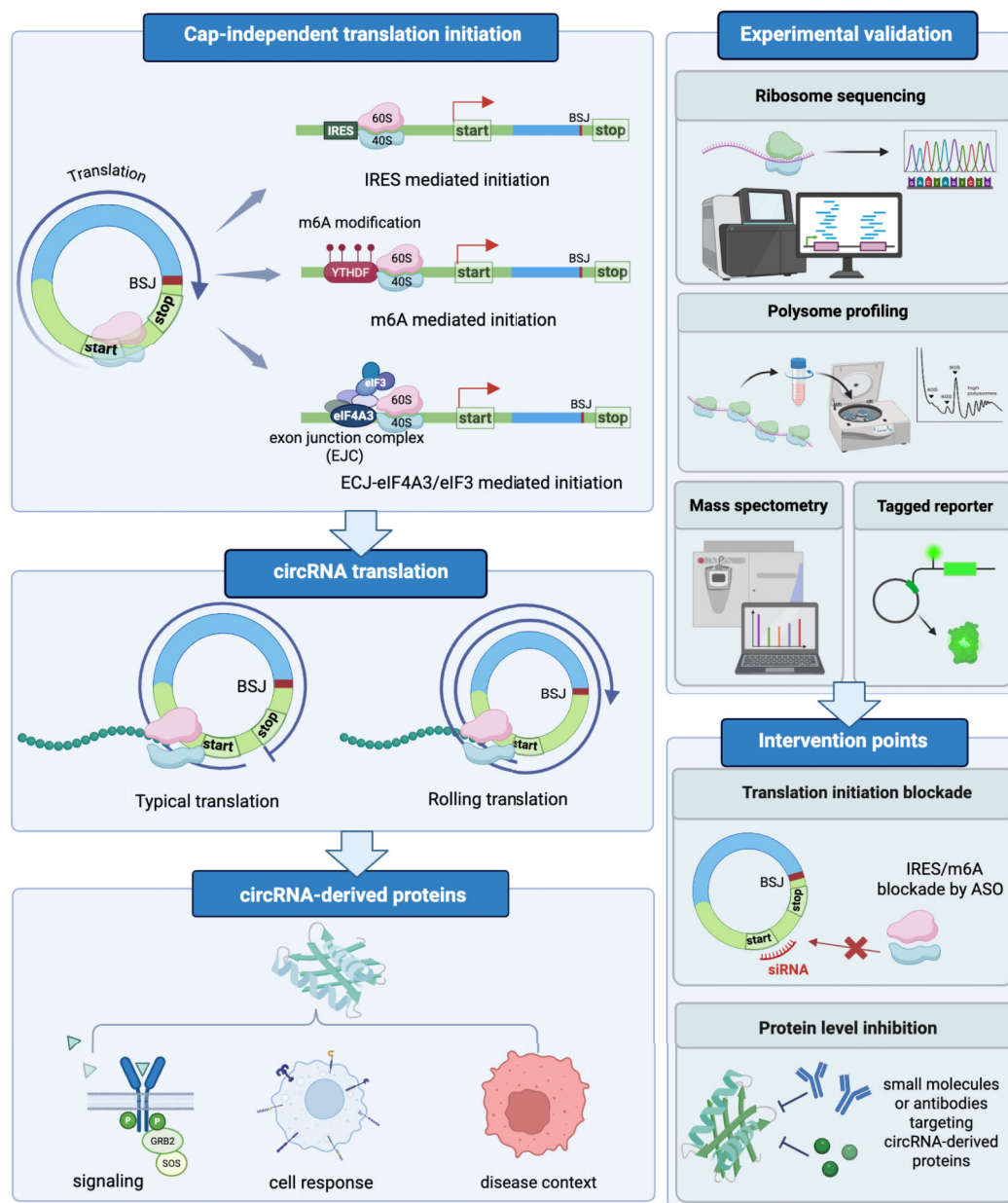


Figure 3 Cap-independent circRNA translation and therapeutic intervention points. CircRNAs can be translated in a cap-independent manner through multiple mechanisms, including IRES-mediated initiation, m⁶A-dependent initiation, and exon junction complex (EJC)-associated recruitment of the translation machinery. Translation proceeds across the BSJ and can generate peptides or proteins through typical or rolling translation modes. Experimental validation of circRNA translation includes ribosome profiling, polysome analysis, mass spectrometry, and tagged reporter assays. Therapeutic strategies may target translation initiation or directly inhibit circRNA-derived proteins using RNA-based or protein-directed approaches. Created in BioRender. Wu, N. (2026). BioRender.com/454d9mi

focused RNA strategies, including siRNAs or ASOs targeting IRES or m⁶A-dependent initiation regions, may reduce peptide production without degrading the circRNA itself [16, 37, 103]. Collectively, these approaches offer reversible and tunable control over circRNA-derived protein expression, consistent with precision intervention strategies.

A major challenge in this therapeutic area is the reliable identification and validation of functional peptides encoded by circRNAs. Experimental confirmation usually requires combining ribosome profiling, mass spectrometry, and epitope-tagged reporter

assays to distinguish true translation products from nonspecific or low-level translation events (Fig. 3) [14, 15]. In addition, evaluating whether circRNA-derived peptides are suitable drug targets requires careful analysis of their subcellular localization and their role in disease processes. Together with RNA-based strategies, approaches that target circRNA-derived peptides and proteins broaden the circRNA therapeutic landscape. By acting at the level most directly linked to biological functions, these strategies complement RNA knockdown and further support the use of circRNAs as precision therapeutic targets.

Translational potential of circRNAs

The therapeutic strategies outlined above highlight the importance of understanding when and how circRNAs exert functional effects at the protein level. To effectively target circRNA-derived peptides or selectively regulate their production, it is essential to define the molecular mechanisms involved in circRNA translation and to establish the role of translational output in disease pathogenesis.

Evidence of protein/peptide translation from circRNAs

As mentioned in the “CircRNAs in Pathophysiology” section, accumulating evidence indicates that a subset of circRNAs can be translated through cap-independent mechanisms, relying on internal RNA elements or RNA-protein complexes rather than the canonical 5' cap-dependent initiation pathway. Multiple initiation modes have been described, with IRES, N⁶-methyladenosine (m⁶A)-dependent initiation, and exon-junction associated translation emerging as the best-characterized mechanisms (Fig. 3).

IRES-mediated translation

IRES-mediated initiation was among the earliest mechanisms proposed for circRNA translation. Using ribosome profiling in *Drosophila*, Pamudurti *et al.* demonstrated that several endogenous circRNAs associate with ribosomes and are translated *in vivo*, providing early genome-wide evidence for circRNA translation that is driven by internal RNA elements rather than 5' cap-dependent initiation [15]. In mammalian systems, Legnini *et al.* showed that circZNF609 is translated in a splicing-dependent manner and that translation relies on internal sequences capable of driving cap-independent initiation, particularly during myogenic differentiation [14]. More recently, two studies systematically analyzed short IRES-like elements embedded in circRNAs and demonstrated that such motifs are sufficient to initiate translation in circular contexts. This supports the notion that IRES-like activity is relatively common among translatable circRNAs [34, 97]. Together, these studies support IRES-mediated initiation as a major mechanism for circRNA translation, particularly under conditions where cap-dependent translation is compromised.

m⁶A-dependent translation initiation

A second, well-supported initiation mode involves m⁶A-dependent translation. In a seminal study, Yang *et al.* demonstrated that a single internal m⁶A modification is sufficient to initiate circRNA translation and requires the m⁶A reader YTHDF3 and the non-canonical initiation factor eIF4G2 [16]. Building on this work, Di Timoteo *et al.* showed that m⁶A deposition on circRNAs is dynamically regulated and contributes to translational control, linking circRNA translation to epitranscriptomic remodeling during cellular stress responses [104]. A recent study in glioblastoma demonstrated that the m⁶A-modified circRNA circMET associates with the m⁶A reader YTHDF2. Knockdown of YTHDF2 reduced production of the circMET-derived peptide MET404 without altering circRNA levels, implicating m⁶A-dependent mechanisms in endogenous circRNA translation [105]. These studies collectively establish m⁶A as a context-responsive initiation signal for circRNA translation.

Exon junction complex-associated initiation (EJC-eIF4A3/eIF3)

Besides IRES- and m⁶A-mediated mechanisms, more recent work has identified an initiation mechanism linked to the exon junction complex (EJC). CircRNAs retain exon-exon junctions generated by back-splicing, providing a distinct structure for EJC deposition compared with linear mRNAs. Direct evidence for this mechanism was provided by Lin *et al.*, who showed that canonical splicing promotes EJC deposition on endogenous circRNAs, enhancing ribosome association and translational output without significantly altering circRNA abundance. Disruption of splicing or EJC components reduced circRNA translation, and translation of circSDHAF2 was shown to contribute to tumor-associated phenotypes in colorectal cancer cells [106]. Mechanistic insight was further advanced by Chang *et al.*, who identified a direct interaction between the EJC core factor eIF4A3 and the translation initiation factor eIF3g, facilitating internal initiation on circRNA templates. Transcriptome-wide analyses indicated that efficient polysome association of endogenous circRNAs can depend on eIF4A3, supporting a model in which EJC components link circRNAs to the eIF3 complex to promote ribosome recruitment [107]. In parallel, Song *et al.* identified the eIF3-associated subunit eIF3j as a negative regulator of circRNA translation, showing that eIF3j limits ribosome engagement and peptide production from circRNAs without altering RNA levels, and that this inhibition is modulated under stress conditions [108]. Together, these studies support the existence of an EJC-eIF3-dependent initiation pathway in which EJC deposition facilitates circRNA translation, while associated initiation factors dynamically regulate translational output.

Elongation modes of circRNA translation: canonical and rolling-circle translation

Following translation initiation, circRNAs can support distinct elongation modes depending on their sequence. CircRNAs that contain a defined open reading frame (ORF) with an in-frame stop codon undergo canonical elongation, yielding a single peptide or protein product. In contrast, circRNAs that lack an in-frame stop codon can undergo rolling-circle translation, a process in which ribosomes repeatedly traverse the circular template to generate repetitive polypeptides. A biologically relevant example of endogenous rolling translation was reported by Liu *et al.*, who identified a circRNA derived from the EGFR locus (circ-EGFR) in glioblastoma that contains an infinite ORF and produces a polymeric EGFR variant (rtEGFR) through rolling translation. The resulting repetitive protein complex interacts with membrane EGFR, stabilizes receptor signaling, and promotes tumorigenicity in glioblastoma models, demonstrating that rolling translation of an endogenous circRNA can generate functional protein products with disease relevance [109]. Recently, this mechanism has been more extensively explored using engineered circRNA systems to study circRNA translation dynamics and its use as platforms for sustained protein expression [110, 111]. Available evidence suggests that canonical elongation predominates among translatable endogenous circRNAs, whereas rolling-circle translation represents a specialized elongation mode that can generate biologically active products in select endogenous contexts and can be efficiently harnessed through rational circRNA engineering.

Functional implications of circRNA-derived peptides

Accumulating evidence indicates that circRNA-derived peptides and proteins can exert biologically meaningful functions in disease contexts, particularly in cancer and cardiovascular disorders.

In oncology, several circRNA-encoded proteins have been shown to directly modulate oncogenic signaling pathways, tumor cell behavior, and therapeutic response. For example, a circRNA derived from the CDH1 locus encodes C-E-Cad, a truncated E-cadherin variant that activates EGFR-STAT3 signaling and promotes glioblastoma tumorigenicity [39]. Similarly, circEGFR undergoes rolling translation to produce a polymeric EGFR variant (rtEGFR) that sustains EGFR signaling by limiting receptor internalization, thereby enhancing glioblastoma growth [109]. Additional studies have identified circRNA-encoded proteins such as MET404 (from circMET), which promotes glioblastoma progression [105], and circMAP3K4-455aa, which modulates apoptotic responses and contributes to chemoresistance in hepatocellular carcinoma [112]. More recently, a circRNA-derived peptide encoded by circPIAS1 was shown to regulate ferroptosis and immune checkpoint therapy responsiveness, linking circRNA translation to cancer immunotherapy-relevant pathways [113]. Collectively, these studies demonstrate that circRNA-derived proteins can act as active signaling modulators rather than translational byproducts, often influencing disease phenotypes through dominant or non-canonical mechanisms.

Emerging evidence also supports functional roles for circRNA-encoded peptides in cardiovascular disease, although the number of well-characterized examples remains limited. In cardiac hypertrophy, a truncated peptide derived from circCDYL was shown to exacerbate pathological remodeling by modulating transcriptional and metabolic pathways in cardiomyocytes [99]. Similarly, translation of circSLC8a1 produces a protein isoform implicated in cardiac remodeling and calcium-handling-related dysfunction [114]. Beyond the myocardium, circRNA-derived proteins have also been implicated in vascular and arrhythmic diseases: a peptide encoded by circSETD2 suppresses vascular smooth muscle cell proliferation and attenuates pathological vascular remodeling [115], while circNAB1-356 was reported to mitigate atrial fibrillation-associated inflammation and fibrosis [54].

Taken together, these findings indicate that peptides encoded by circRNAs can directly contribute to the initiation and progression of disease, often through mechanisms that differ from those of proteins produced from linear mRNAs. Due to their functional effects depending on cell type and disease stage, circRNA-derived proteins, as distinct functional mediators and potential therapeutic targets, warrant careful validation of their translation and disease-specific roles.

Therapeutic design opportunities

Engineering circRNAs for therapeutic peptide/protein expression

Cap-independent translation of circRNA has led to growing interest in using synthetic circRNAs as platforms for therapeutic protein expression. Unlike endogenous circRNAs, which are

mainly studied for regulatory roles, engineered circRNAs are intentionally designed to optimize protein production, stability, safety, and control [116, 117]. These constructs typically include optimized ORF, IRESs or m⁶A-dependent initiation elements, and flanking sequences that promote efficient circularization, resulting in stable and efficient protein expression in target cells [118]. Compared with linear mRNA therapeutics, synthetic circRNAs offer several potential advantages that are supported by early experimental evidence. Multiple studies have demonstrated that synthetic circRNAs can drive durable protein expression *in vitro* and *in vivo*, often exceeding the persistence of comparable linear mRNA constructs when appropriately engineered [116, 119].

The covalently closed structure of circRNAs results in longer intracellular persistence and more sustained protein expression than linear mRNAs [120, 121]. Moreover, the lack of free 5' and 3' ends may reduce innate immune activation under certain conditions, although reported immune responses vary and remain dependent on sequence features, chemical modifications, and purification methods [119, 122]. From a translational perspective, synthetic circRNAs have therefore been explored mainly as expression platforms in vaccination, and immunotherapy, where sustained antigen or therapeutic protein production may be beneficial [119, 123].

These features make circRNAs attractive for applications that require durable protein expression. However, achieving tissue- or disease-specific expression remains a key challenge for circRNA-based therapeutic design. Several strategies are being explored to enhance specificity, including the use of cell type-specific delivery systems, incorporation of tissue-specific regulatory elements, and engineering circRNAs whose translation is activated under defined cellular conditions, such as stress- or disease-associated signaling states [116, 124, 125]. Together, advances in circRNA engineering and delivery are beginning to establish synthetic circRNAs as a viable platform for therapeutic peptide and protein expression. While most applications remain in preclinical development, early translational efforts highlight the potential of circRNAs to complement or extend existing mRNA-based therapies, particularly in settings where sustained and regulated protein expression is desirable.

RNA depletion approaches targeting circRNA-derived proteins

Current strategies to inhibit circRNA-derived peptide or protein production have relied primarily on RNA depletion approaches, in which the circRNA transcript itself is reduced, thereby limiting the availability of the template required for translation. These methods do not selectively target translation per se but instead suppress circRNA expression upstream, resulting in concomitant loss of circRNA-encoded protein products. Despite this limitation, RNA depletion strategies have provided critical proof-of-principle evidence that circRNA-derived proteins are functionally relevant and therapeutically actionable.

Several disease-relevant studies illustrate this principle using siRNA-based circRNA knockdown. In glioblastoma, Liu *et al.* demonstrated that siRNAs targeting the BSJ of circEGFR reduced circEGFR levels and concomitantly diminished production of the rolling-translated EGFR variant (rtEGFR), leading to attenuation of EGFR signaling and tumorigenic phenotypes [109]. Similarly,

Zhong *et al.* employed siRNA-mediated depletion of a translatable circRNA isoform derived from MET, resulting in reduced expression of the circRNA-encoded protein MET404 and suppression of glioma progression [105]. In both cases, suppression of circRNA-derived protein output was achieved through circRNA depletion rather than selective inhibition of translation, indicating the feasibility of RNA-level intervention when circRNA-encoded proteins drive disease phenotypes.

More recently, CRISPR-based approaches have provided direct genetic evidence linking circRNA expression to circRNA-derived protein production. Using CRISPR/Cas9-mediated disruption of intronic sequences required for back-splicing, Zhong *et al.* selectively suppressed circMET biogenesis without altering linear MET mRNA, resulting in marked loss of MET404 protein and reduced tumor growth [105]. In a distinct biological context, Guo *et al.* generated CRISPR knockout models of the protein-coding circRNA circZfh1 in *Drosophila*, demonstrating complete elimination of its encoded protein CRAV and consequent impairment of antiviral immunity [126]. These studies establish that genetic disruption of circRNA expression can directly abolish circRNA-derived protein production and phenotypic output.

Together, siRNA- and CRISPR-based depletion studies provide compelling evidence that circRNA-derived peptides and proteins depend on sustained circRNA expression and can be effectively suppressed by targeting the RNA template. While these approaches do not distinguish translational from non-translational circRNA functions, they represent the most robust experimental strategies currently available for interrogating and modulating circRNA-encoded protein activity in disease models.

Synthetic circRNAs as stable RNA therapeutics

Beyond their use as expression platforms for peptides and proteins, synthetic circRNAs can also function directly as RNA-based therapeutics. In this context, the therapeutic effect arises from the RNA molecule itself rather than from a translated product. Engineered circRNAs may act by sequestering microRNAs, altering RNA-protein interactions, or serving as decoys or scaffolds. Lavenniah *et al.* constructed engineered circRNA sponges to sequester target miRNAs and used *in vivo* in a pressure-overload-induced cardiac hypertrophy mouse model to improve cardiac outcomes [127]. A recent study delivered synthesized short double-stranded region-containing circRNAs (ds-cRNAs) by LNPs to the spleen of the mice with psoriasis. It is found that ds-cRNAs inhibited protein kinase R (PKR) activity and consequently attenuated the psoriasis phenotypes [128]. These observations indicate that the synthetic circRNAs may influence gene expression and cellular pathways without relying on protein production.

As with other RNA-based therapies, effective delivery remains a major challenge for synthetic circRNAs when used as RNA therapeutics. Achieving appropriate tissue uptake, limiting off-target effects, and ensuring consistent intracellular localization will be critical for clinical translation. In addition, standardized approaches for manufacturing, quality control, and potency assessment will be required to support regulatory evaluation. Addressing these challenges will help define the role of synthetic circRNAs as stable and controllable RNA therapeutics and provide a foundation for the discussion of delivery platforms in the following section.

Delivery systems for circRNA-based therapeutics

Efficient and precise delivery is a key factor in the success of circRNA-based therapeutics. The circRNA stability alone is not sufficient, as therapeutic efficacy depends on delivering circRNA molecules or circRNA-targeting agents to the appropriate tissues and cellular compartments at adequate levels. Experience from mRNA-, siRNA-, and ASO-based therapies offers important guidance for evaluating delivery strategies for circRNA applications.

Viral delivery systems

Viral vectors, especially adeno-associated virus (AAV) and lentiviral vectors, have been widely used for long-term gene expression and have been studied as approaches to deliver circRNAs [129, 130]. AAV vectors offer high transduction efficiency and favorable safety profiles in multiple tissues and have been used in preclinical studies to express engineered circRNAs *in vivo* [129, 131, 132]. For example, Meganck *et al.* effectively delivered translatable circRNAs intravenously via recombinant adeno-associated viral (rAAV) vectors and successfully expressed the circRNAs in the heart, liver, brain, and eyes of the mice [129]. In another study, Zeng *et al.* used the AAV9-mediated delivery system to express circMAP3K5 in vascular smooth muscle cells in the injured femoral arteries and significantly reduced intimal hyperplasia [130]. In the same study, lentiviral vectors were employed to deliver the circMAP3K5 to the coronary artery smooth muscle cells *in vitro*. Lentiviral vectors can accommodate larger inserts and enable stable genomic integration, although their permanent nature raises additional safety considerations for therapeutic applications [130, 133, 134]. However, a study specifically tested different methods for stable circRNA overexpression and reported that lentiviral delivery of circRNA expression constructs produced low levels of circRNA expression in cells [135]. At present, the use of lentiviral vectors for circRNA delivery *in vivo* remains limited, likely reflecting technical constraints related to circRNA biogenesis during viral vector production, as well as broader safety considerations associated with permanent genomic integration.

Lentiviral and adeno-associated viral vectors differ in how well they accommodate circRNA expression cassettes. While both platforms are established for gene delivery, lentiviral vectors require efficient packaging of unspliced genomic RNA during vector production, which can be difficult to reconcile with circRNA constructs that depend on strong splice signals or intronic repeats to promote back-splicing. These features may reduce viral yield or lead to unpredictable circRNA expression after integration. In contrast, circRNA delivery using AAV has been more widely explored *in vivo*, whereas lentiviral approaches remain less validated for this purpose. Future vector engineering efforts may help clarify whether lentiviral systems can be adapted to support reliable circRNA expression in animal models.

Non-viral delivery systems

Concurrently, non-viral delivery systems, particularly LNPs, have emerged as versatile platforms for RNA therapeutics. LNPs have been clinically validated for mRNA and siRNA delivery and are

increasingly explored for circRNA delivery due to their scalability and transient expression profiles [119, 124]. Polymer-based nanoparticle systems and EV-derived carriers have been explored as alternative non-viral platforms for RNA delivery in both preclinical and early clinical studies. Polymer-based nanoparticles, including ligand-modified and PEGylated formulations, have demonstrated the capacity to deliver RNA cargos *in vivo* and in human trials [136]. Similarly, EV-based delivery systems have shown promise in preclinical models. Surface engineering strategies or careful selection of donor cell types can achieve tissue-enriched delivery and, in some settings, more favorable immunological profiles, as demonstrated by exosome-mediated RNA delivery in brain and pancreatic cancer models [137, 138]. Other than lipid- and polymer-based carriers, inorganic nanoparticle platforms, particularly PEG-functionalized gold nanoparticles, have been explored as alternative non-viral delivery systems for circRNA-related cargos. Unlike LNPs, gold nanoparticle systems rely on surface chemistry rather than encapsulation and have been used in preclinical mouse models to deliver circRNA expression plasmids or circRNA-targeting siRNAs, resulting in measurable alternation of disease phenotypes [94]. Although these studies demonstrate feasibility, gold nanoparticle-based delivery remains at an early exploratory stage relative to lipid-based platforms and requires further optimization and validation.

Non-viral delivery systems differ less in whether they can carry RNA than in how they balance clinical readiness, targeting control, and manufacturing complexity. LNPs are currently the most practical option because they combine scalable production with a strong translational track record from mRNA and siRNA therapeutics, but their biodistribution is still relatively formulation-driven and often biased toward the liver [139]. Polymer-based nanoparticles offer greater design flexibility, including surface and ligand modification, but this flexibility can make formulation performance less consistent and standardization more difficult [140, 141]. EV-based carriers are attractive because of their biological origin and potential for tissue-enriched delivery, as illustrated by engineered systems developed for pancreatic and brain targeting [142, 143]. However, their translational advantages are still limited by challenges in cargo loading, batch consistency, standardized isolation, and large-scale manufacturing [144, 145]. Gold nanoparticles have provided useful proof-of-concept platforms for delivering circRNA-related cargos in preclinical models, but their translational development remains less advanced than that of lipid-based RNA delivery systems [94, 146].

At present, direct comparative studies evaluating viral versus non-viral delivery for circRNA therapeutics are limited. Consequently, selection of delivery platforms for circRNA applications is largely guided by lessons from other RNA modalities, as well as by considerations of tissue specificity, duration of expression, and safety requirements (Fig. 4).

Precision therapy approaches

With multiple delivery platforms now controlling circRNA expression *in vivo*, an important next step is to consider how these technologies can be deployed in a precision medicine context. Beyond the feasibility of delivery, effective clinical translation will depend on identifying the right patients, selecting appropriate circRNA

targets, and integrating circRNA-based interventions with existing therapeutic strategies. In this section, we discuss emerging approaches that leverage circRNA expression profiles, combination treatment strategies, biomarker-guided patient stratification, and computational tools to support more precise and individualized circRNA-directed therapies (Fig. 5).

Patient-specific RNA signatures: stratification by circRNA profiles

The cell type- and disease-specific expression patterns of circRNAs have prompted interest in their use as molecular signatures for patient stratification. Large-scale transcriptomic studies have demonstrated that circRNA expression profiles vary across cell type, tissues/organs, developmental stages, and disease states, including cancer and cardiovascular disorders, often independently of their linear host transcripts [1, 2, 147]. Essentially, circRNAs are highly stable in biofluids such as plasma and serum, enabling their detection in liquid biopsy settings and supporting their evaluation as noninvasive biomarkers for disease classification and prognosis [7, 148]. Several studies have reported associations between circulating circRNA signatures and clinical outcomes, suggesting that circRNA profiling may complement existing genomic and proteomic biomarkers for patient stratification and risk assessment [72, 147]. However, most circRNA biomarker studies remain retrospective or exploratory, and standardized workflows for circRNA normalization and validation are still developing.

Mixers and combinational therapies

The rapid progress of RNA therapy has demonstrated that RNA-level interventions can be safely and effectively integrated into modern therapeutic pipelines [149, 150]. While circRNA-targeting approaches remain at an early stage of development, the experience from established RNA drugs provides a strong foundation for considering circRNAs as part of multimodal therapeutic strategies. In practice, ASOs and siRNAs are often developed as stand-alone agents but are frequently evaluated and applied alongside conventional treatment in clinical settings. This experience indicates that RNA-based drugs can be pharmacologically compatible with other therapeutic modalities, including small-molecule inhibitors and biologics, even if systematic combination trials are not always explicitly designed to test synergy. From a conceptual and translational perspective, circRNA-targeting approaches offer opportunities for layered intervention. For example, suppression of circRNA-derived peptide production could, in principle, complement therapies acting on downstream signaling pathways or disease-relevant effectors. While such combinational strategies have not yet been directly tested for circRNA therapeutics, they are well aligned with paradigms already used in precision medicine, where targeting multiple nodes within a disease pathway is common. Taken together, the success of combination strategies in the broader RNA therapeutic field supports a positive outlook for the future integration of circRNA-directed agents into multicomponent treatment regimens, pending systematic preclinical and clinical evaluation.

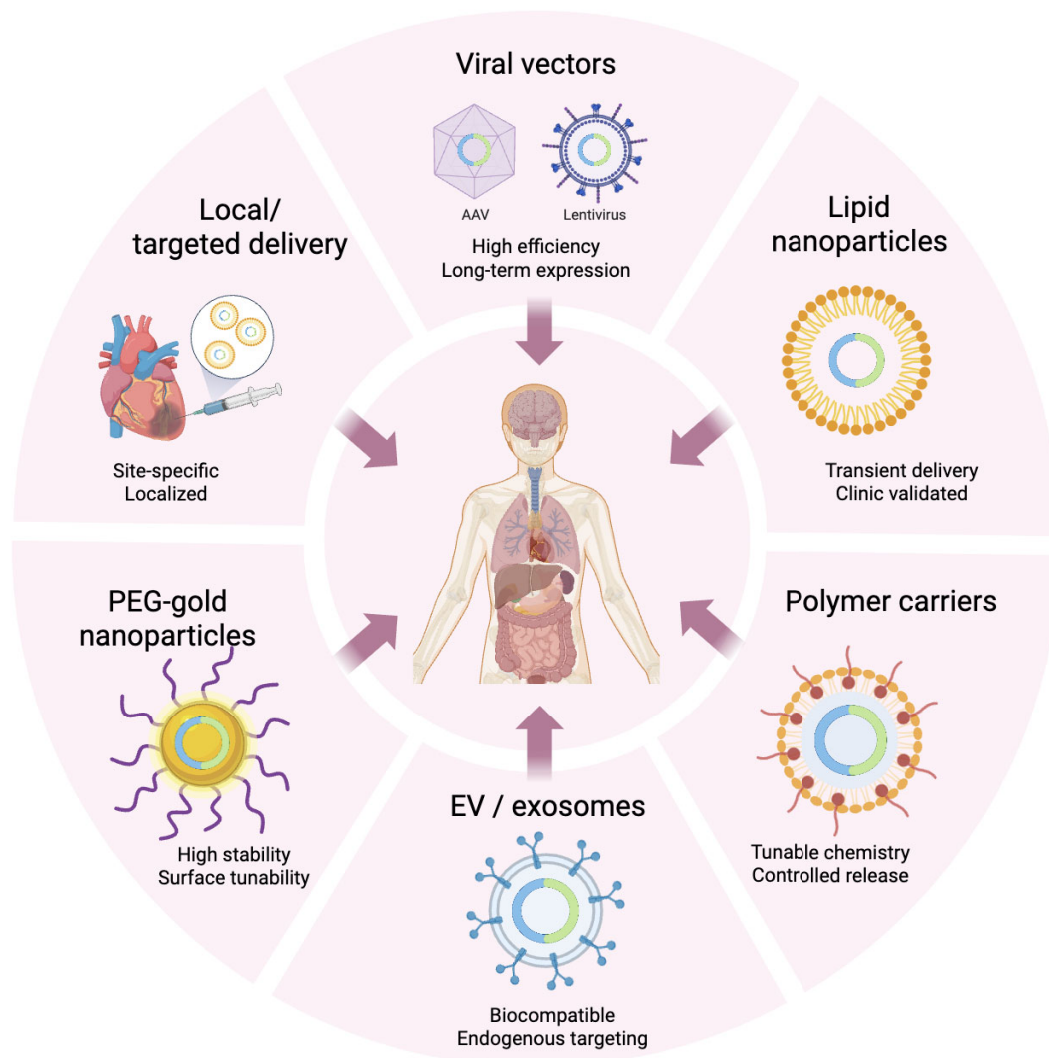


Figure 4 Delivery platforms for circRNA-based therapeutics. Overview of major delivery platforms for circRNA-based therapeutics. Viral vectors, including AAV and lentivirus, enable efficient gene transfer and sustained expression. LNPs support transient delivery and have established clinical utility. Polymer-based carriers offer tunable chemistry and controlled release profiles. EVs and exosomes provide biocompatible carriers with endogenous targeting potential. PEGylated gold nanoparticles afford high stability and surface functionalization flexibility. Local or targeted delivery approaches allow site-specific and localized administration. These platforms illustrate the range of options available for delivering circRNAs or circRNA-targeting agents, highlighting the need to match delivery strategy to therapeutic goals and target tissues. Created in BioRender. Wu, N. (2026). BioRender.com/el43vss

Computational and AI-assisted approaches in circRNA precision medicine

Advances in computational biology and machine learning (ML) have already had a significant impact on RNA research by supporting large-scale annotation, target prioritization, prediction of RNA secondary structure and function, as well as RNA-small molecule interaction and aptamer discovery [151]. In the circRNA field, bioinformatic tools have been successfully developed to identify circRNAs from transcriptomic data and to predict features relevant to translational potential, including ORFs and internal initiation elements [152–154]. These approaches have expanded the catalog of candidate circRNAs for functional investigation and therapeutic consideration. Similarly, computational frameworks integrating sequence features with RBP datasets have been applied to infer circRNA–protein interaction networks [155,

156]. Although such predictions require downstream biochemical confirmation, they have proven effective in guiding discovery efforts in other areas of RNA biology and are increasingly refined as higher-quality datasets become available. AI-driven integration of multiomics data, including circRNA expression, epitranscriptomic modifications, proteomics, and clinical phenotypes, has the potential to support patient-specific target prioritization. Comparable strategies are already being explored in precision oncology and genetic medicine [157, 158], and their extension to circRNA biology represents a natural progression rather than a conceptual leap. While the application of ML-guided decision-making to circRNA therapeutics remains at an early stage, ongoing improvements in data quality and model interpretability are likely to accelerate progress. Through data-driven target prioritization, assessment of functional relevance, patient stratification, and biomarker discovery, AI/ML integration is expected to accel-

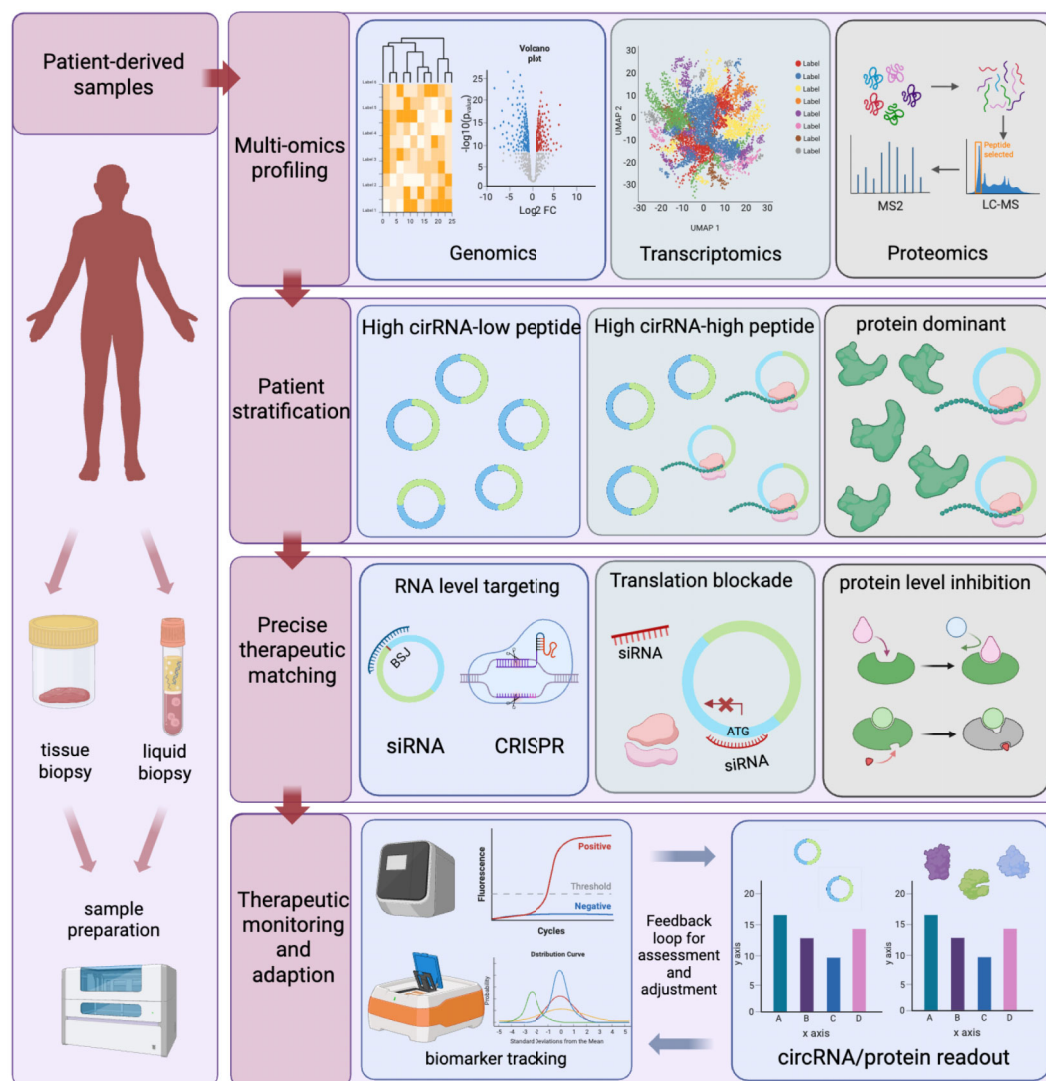


Figure 5 Framework for circRNA-based precision medicine. This framework illustrates how circRNAs may function as both biomarkers and therapeutic effectors to support more precise and individualized clinical intervention. Patient-derived samples, including tissues and biofluids, are analyzed to define disease-associated circRNA profiles. These data inform target selection and choice of therapeutic modality, such as ASO- or siRNA-based approaches, peptide-directed strategies, or synthetic circRNAs, and can be integrated with existing treatment regimens. Computational and machine learning tools support the prediction of circRNA structure, translational potential, and RNA–protein interactions, enabling target prioritization and personalized therapeutic design. Created in BioRender. Wu, N. (2026). BioRender.com/1r0z17s

erate the clinical development of circRNA-based diagnostics and therapeutics.

Clinical landscape and ongoing trials

Clinical translation of RNA therapeutics is now well established, led by chemically modified ASOs and siRNA drugs that achieve durable target modulation in humans with increasingly refined delivery strategies, such as GalNAc conjugates for hepatocyte targeting and LNPs for broader applications [159]. Building on this foundation, non-coding RNA-directed programs have also reached the clinic, most notably miRNA-targeting agents. For example, the miR-122 inhibitor miravirsen showed antiviral activity in a Phase 2a study in chronic HCV patients, providing early proof that mod-

ulating regulatory RNAs can yield clinical pharmacodynamic effects (ClinicalTrials.gov number: NCT01200420) [160]. In oncology, the liposomal miR-34a mimic MRX34 represented a landmark first-in-human miRNA replacement approach, although its trial was terminated due to immune-related serious adverse events, demonstrating the importance of immunotoxicity monitoring and dose/setting selection for systemic RNA medicines (ClinicalTrials.gov number: NCT01829971) [161].

Against this broader RNA-therapy backdrop, circRNA therapeutics have begun to enter first-in-human evaluation, though the landscape remains early and heterogeneous. The clearest example is RXRG001 (RiboX Therapeutics), which has been described as the first-in-human circRNA therapeutic for radiation-induced xerostomia/hyposalivation. Trial registration and independent trial summaries indicate that RXRG001 is administered locally to the parotid ducts, with assessment of preliminary efficacy and safety

(ClinicalTrials.gov number: NCT06714253). Beyond RXRG001, clinical trial registries also list additional circRNA-based interventions as pilot or early-phase study, including epicardial circular RNA HM2002 evaluated in patients undergoing coronary artery bypass graft (CABG) surgery for ischemic heart failure (ClinicalTrials.gov number: NCT06621576), and an exenatide circular RNA-LNP injection (CR059) study assessing safety, pharmacokinetic, pharmacodynamic, and immunogenicity in people with type 2 diabetes (ClinicalTrials.gov number: NCT07347080). In parallel, early investigator-initiated cancer immunotherapy studies are exploring circular-RNA-linked antigen concepts. Such trials include evaluating a vaccine strategy involving circFAM53B-related tumor antigens (ClinicalTrials.gov number: NCT07245901). Preclinical studies of circSCMH1 have demonstrated therapeutic efficacy in both rodent and non-human primate models of stroke, with supportive associations in human patient samples. This study provides a strong translational rationale for progression toward early-phase clinical testing despite the absence of a registered circRNA trial for stroke to date [162].

Overall, the current clinical picture suggests that circRNA is moving from platform maturation toward early clinical testing, with the near-term pace likely shaped by (i) delivery tractability for specific tissues, (ii) immunogenicity/innate sensing management, and (iii) manufacturing and analytical standards needed for consistent circular RNA drug substance and formulated product across sites and lots.

Challenges, opportunities, and future directions

Breakthroughs in circRNA biology and successful preclinical studies demonstrated the therapeutic value of circRNA. However, several barriers remain before broad clinical translation can be achieved. Some of these challenges overlap with those faced by other RNA therapeutics, while others are related to the unique structure, biogenesis, and multifunctional roles of circRNAs. Identification of circRNAs based solely on RNase R digestion may yield false-positive or false-negative results.

Efficient and precise delivery continues to be the central challenge, as successful clinical application will require tighter control over biodistribution and dosing. Given the tissue- and cell type-specific features of circRNAs, delivery strategies must be tailored to the target organ while limiting off-target effects.

Another important consideration is functional specificity. Since circRNAs often participate in multiple regulatory processes, global modulation of circRNA levels may lead to unintended consequences. Especially, for those low-abundance circRNAs, whether they are functional molecules or just splicing noise must be carefully evaluated. For those circRNAs that are not well conserved across species, questions of evolutionary importance may be raised.

More selective approaches that target circRNA-derived proteins offer promise but require further validation *in vivo*. In particular, the abundance of the translated proteins within the tissues of interest may suggest the efficiency and functional relevance of the process. Manufacturing and standardization remain significant challenges for clinical translation. Scalable production of high-purity circRNA with consistent circularization efficiency and reproducible biological activity remains an evolving area.

In the future, several opportunities may accelerate the development in the field. Integration of multiomics data, including transcriptomic, proteomic, and ribosome profiling datasets, can improve the identification of circRNAs with disease-relevant functions. Advances in computational modeling and ML approaches are also expected to support the prediction of circRNA structure, interaction partners, and translational potential, thereby prioritizing candidates with higher chances of clinical success. Moreover, continued improvement of delivery technologies and conditional expression systems may promote more precise, context-dependent regulations of circRNA activity. As early human studies begin to emerge and therapeutic toolkits for selective circRNA manipulation continue to mature, circRNAs are well-positioned to contribute meaningfully to the next generation of precision RNA therapeutics.

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Conflicts of interest

The authors declare no conflict of interest. In addition, as the Editorial Board Member of *Precision Clinical Medicine*, the corresponding author Burton B. Yang was blinded from reviewing and making decision on this manuscript.

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