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From rare to prevalent: dawn of the RNA therapeutics era

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Two decades ago, RNA was merely a humble 'messenger' delivering genetic instructions from DNA to proteins in textbooks. Today, it has evolved into a therapeutic modality and stands at the forefront of a biomedical revolution. RNA therapies are now transitioning from addressing the needs of small patient populations with rare diseases, to redefining treatment paradigms for common chronic conditions. This transformation is driven by an exquisitely orchestrated integration of biology, information and computing sciences, chemistry, and materials science.

Traditional small-molecules and antibody drugs generally demonstrate their therapeutic effects by binding to specific protein domains. However, about 85% human disease-related protein targets have long been considered 'difficult-to-drug' or even 'undruggable', due to factors such as flat protein surfaces lacking stable binding pockets, unclear functional ligands, or excessively high affinity for endogenous substrates[1–3]. RNA therapeutics is fundamentally reshaping this landscape. It enables direct targeting of RNA transcripts using modalities like small interfering RNAs (siRNAs), and antisense oligonucleotides (ASOs), which act as molecular scissors to halt pathogenic protein synthesis at the mRNA level. This upstream intervention strategy circumvents the limitations of conventional target recognition and enables targeting previously inaccessible key disease drivers. Beyond this, a paradigm-shifting integration with degradation strategies is emerging, exemplified by the ribonuclease-targeting chimera (RIBOTAC) system. RIBOTAC is a bifunctional molecule that binds a specific target RNA while simultaneously recruiting a ribonuclease (e.g., RNase L) to trigger localized RNA cleavage[4–6]. Crucially, this mechanism unlocks the indirect targeting and degradation of RNA-binding proteins (RBPs) and RNA-protein complexes (RNPs) by destroying their essential RNA scaffold. Thereby, it converts undruggable protein targets into druggable RNA proxies, paving the way for eliminating previously intractable pathogenic complexes[7,8].

This strategic expansion of the targetome was a key enabler for the clinical translation of RNA therapies. The development of RNA-based treatments marks a significant milestone in medicine, starting from their initial success in treating rare diseases. To date, the US Food and Drug Administration (FDA) has approved several RNA therapies, including 11 ASOs, seven siRNAs, two aptamers, and two mRNA-based products[9]. Many of these early treatments focused on rare health conditions. For example, Patisiran is designed for a rare condition called hereditary transthyretin-mediated amyloidosis[10], and Nusinersen is used for spinal muscular atrophy[11]. These pioneering RNA medicines provided conclusive evidence that precision intervention at the RNA level could correct the internal instructions.

In recent years, the success of the Moderna and Pfizer–BioNTech COVID-19 vaccines has pioneered the expansion of mRNA technology into chronic disease therapeutics. A leading example is Inclisiran, a siRNA-based therapy that targets the PCSK9 protein[12]. Inclisirian enables a sustained reduction in low-density lipoprotein cholesterol with just two subcutaneous injections per year. The ultra-long-lasting effect significantly improves the prevention and management of cardiovascular diseases, transforming how they are prevented and managed, and enhancing medication adherence. This marks only the beginning. A growing pipeline of RNA candidates is progressing through clinical development for prevalent conditions such as non-alcoholic steatohepatitis (NASH), hypertension, and hepatitis B[13,14].

Additionally, RNA-based therapeutics have demonstrated growing promise in oncology, with clinical advances in areas including cancer vaccines and targeted therapies[15–17]. Notably, a Phase 2b clinical trial evaluating the combination of the individualized neoantigen mRNA vaccine mRNA-4157 with pembrolizumab vs pembrolizumab alone in patients with resected melanoma demonstrated that the combination therapy prolonged recurrence-free survival, with comparable and manageable adverse events[16]. Similarly, a Phase I trial investigating an individualized uridine mRNA-lipoplex neoantigen vaccine (autogene cevumeran) in patients with pancreatic ductal adenocarcinoma (PDAC) showed that, at 18 months of follow-up, those who mounted a vaccine-induced immune response (responders) experienced longer median recurrence-free survival compared to non-responders[17]. These promising findings underscore the potential of mRNA-based therapies as a new frontier in oncology, paving the way for more personalized and effective cancer treatments.

Nevertheless, the clinical translation of RNA therapeutics continues to face two major challenges. One is sequence-dependent immune activation, and the other is suboptimal delivery efficiency, particularly regarding endosomal escape and tissue-specific targeting[18,19]. To address them, researchers are employing AI-powered bioinformatics tools for rational RNA sequence design, enabling simultaneous optimization of molecular stability, translational capacity, and immunogenicity profiles. Complementary to this, strategic chemical modifications continue to enhance the biostability and pharmacokinetic properties of RNA constructs in physiological environments. Materials science, through the development of delivery systems such as lipid nanoparticles, has constructed 'molecular transport vessels' capable of accurately delivering drugs to target cells. Therefore, it is the synergistic support of a multidisciplinary team that has advanced RNA drugs from theory to clinical practice.

The full actualization of RNA therapeutics' potential hinges on systematic collaboration across scientific disciplines and healthcare sectors. As these treatments expand into wider clinical applications, their advancement demands coordinated input from researchers, clinicians, regulatory agencies, and payers to establish end-to-end governance frameworks. Critical priorities for the coming decade will include resolving persistent delivery challenges, such as improving endosomal escape and tissue-targeting specificity, and harnessing AI-driven modeling and structural bioinformatics to advance the rational design of RNA molecules. Additionally, integrating RNA

biology with emerging fields such as degradomics, synthetic biology, and immuno-oncology is expected to unlock new paradigms in precision medicine. To support this progress, institutional initiatives will be essential, including interdisciplinary training programs that bridge biology, computation, and engineering, as well as funding models that actively promote convergent research. Through such coordinated efforts, RNA-based technologies may mature into globally accessible, equitable, and sustainable treatment options for patients worldwide.

Author contributions

The draft of the manuscript was prepared by Zhou J and Shu E. Both authors reviewed the results and approved the final version of the manuscript.

Data availability

Not applicable.

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Conflict of interest

The authors declare that they have no conflict of interest.

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