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Editorial

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The current and future landscape of RNA-based therapies and diagnostics

Amid continuous innovation in sequencing and gene-editing technologies combined with enhanced understanding of RNA biology, there has been an increase in RNA-based technologies for the treatment of a wide array of diseases. We discuss some recent work in the field, highlighting the RNA biology and RNA-based applications to medicine collection, which showcases the versatility of RNA for filling numerous gaps in disease treatment and detection.

RNA is a fundamental and multifunctional molecule that serves as the messenger for protein synthesis whilst also forming critical secondary structures, performing key regulatory functions, signaling the presence of pathogens in cells, and more. The flexibility and power of RNA and nucleic acids have driven countless basic and translational studies, with notably 19 small RNAs[1], seven gene replacement therapies[2], and two mRNA vaccines approved for patient use[3]. The continued reduction in sequencing cost and promise of personalized therapies underscores the future potential of RNA-based medicines or nucleic acid therapeutics (NATs), but this also requires proper workflows to be established for design, regulatory approvals, and diligent safety testing. We established the RNA biology and RNA-based applications to medicine collection to highlight these advances, as well as the cross-talk between basic studies of RNA and the translation of these findings to the treatment and prevention of human disease.

The success of NATs is grounded in decades of research building therapies for rare and infectious diseases that rely on small RNAs, such as, but not limited to, anti-sense oligos (ASOs) and small-interfering RNAs (siRNAs). These NATs are therapeutically effective across numerous diseases and tissues[1]. Furthermore, the cooperation between discoveries in basic RNA biology and the timely development of new therapies with a global impact is well illustrated by the development of mRNA vaccines. Years of basic research into RNA immunogenicity, nucleic acid modifications, and advanced formulation paved the way for the approval of mRNA vaccines for SARS-CoV-2. Now, not only are mRNA vaccines clinically advanced for additional viral targets[3], they are also being developed for the treatment of common diseases, such as cancer. To date, cancer mRNA vaccines are in a variety of clinical trial phases, and it is anticipated that reported findings of a combination mRNA vaccine and anti-PD-1 therapy for melanoma will be promising[4].

The design of NATs is also being streamlined with the use of systematic bioinformatic tools combined with high-throughput screening methods. Two recent examples include tools to predict optimal ASO sequences for exon-skipping applications[5] and to predict the activity of chemical modifications on siRNA activity[6]. The versatility of ASOs and siRNAs parallels that of programmable gene-editing therapies, as they may become an option for rare diseases or personalized therapies. However, there are numerous considerations related to variant type, target tissue, and patient benefit that should be considered, and were reviewed recently[2,7].

The discovery and innovation surrounding NATs, including programmable, gene-editing technologies, have unlocked the ability to treat some common diseases as well as rare disorders with limited treatment options. Examples of ASOs designed for individual patients[8] and the recent example of a personalized base-editing therapy used for a severe metabolic disorder[9] illustrate the feasibility of these personalized therapies as well as a workflow for their development. As personalized therapies continue to emerge, emphasis on responsible and ethical use and financial considerations are essential. To this end, in the last few years, the FDA released a draft of guidelines for individualized therapies[10] and numerous international collaboratives, foundations and initiatives have been established, including the N = 1 Collaborative (www.n1collaborative.org), the N-Lorem foundation, the One Mutation One Medicine (https://www.1mutation1medicine.eu/), or the Dutch or Spanish Centers for RNA Therapeutics (https://www.rnatherapy.nl/; https://www.rnatherapy.es). Such international efforts will thus serve to help us enter this exciting era of personalized medicine with careful considerations.

A crucial element of the future potential of RNA-based therapies is continued advances in nucleic acid delivery to cells and specific tissues. A recent review highlighted the challenges with delivery while noting the currently approved therapies for rare diseases[2]. Generally speaking, "naked" NATs are efficiently used locally (eye, CNS, etc.), and carriers or conjugations are needed to access other tissues. Liver targeting using N-acetylgalactosamine (GalNAc) conjugation and some LNPs carrying NATs represent the delivery modalities that are most clinically advanced, but their applicability requires additional research surrounding mitigating side effects[11], optimal administration routes, and different formulations. Given the wide range of RNA and nanoparticle characteristics, predicting effective formulations may benefit from the growing efforts to employ machine learning for LNP design[12]. In addition to different LNP formulations, the addition of cell-specific ligands is a recent strategy for targeting tissues of interest. For example, in preclinical studies, an ASO conjugated to an antigen that specifically binds to muscle cells showed improved targeting and gene correction[13]. A similar approach was recently applied using PD-L1 binding peptides conjugated to LNPs as a mRNA delivery system for tumor-targeting therapies[14].

Amid significant investment in the application of RNA for therapeutics, using RNA for disease prevention and detection is an active area of research. There are immense benefits to having minimally invasive strategies for disease detection, and much attention in recent years has been the application of cell-free DNA (cfDNA) tests during pregnancy and for cancer detection. However, several features of cell-free RNA (cfRNA), including its release from multiple cell types and reflection of dynamic and potentially pathogenic processes in the cell, have driven discussion of cfRNA-based biomarkers. Much of the research efforts focus on microRNAs and other non-coding RNAs, such as long RNAs and circular RNAs[15]. For example, a few recent studies have evaluated a long-noncoding RNA in

colorectal cancer[16] and circular RNAs in retinal pathologies[17]. Technical advances and extensive validation of putative RNA biomarkers are still needed, but continued reduction in sequencing cost and basic studies to characterize cell-free nucleic acid in the context of numerous diseases are likely to increase its outlook.

The rapidly expanding therapeutic and diagnostic applications of RNA are fueled by the interplay between basic scientific discovery and clinical application. Numerous areas of investigation are still needed, notably in the areas of delivery, safety, and ethical and financial considerations. However, new research highlighted in this Collection demonstrates the promise of RNA-based approaches to address major unmet medical needs.

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Author contributions

C.A.F. drafted the initial manuscript. V.A-G. contributed significantly to its revision and finalization for submission in its current form.

Competing interests

The authors declare no competing interests.