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1. Introduction

RNA therapeutics are chemically synthesized biomolecules with broad clinical applications, ranging from correcting inherited mutations to treating cancer, chronic conditions, improving organ transplant outcomes, and infectious disease prophylaxes (Figure 1).

2. Applications of RNA-based therapeutics in medicine

The development of RNA therapeutics has been an intense journey, with numerous stories of success and failure. The potential, and suitability, of recently discovered RNAs stemmed from several Nobel Prize-winning discoveries. For example, the Nobel prize for messenger RNA discovery was awarded to F. Jacob, J. Monod, and A. Lwoff in 1965 [1]. Almost 30 years later, P. Sharp and R. Roberts were presented with the Nobel Prize for the discovery of alternative mRNA splicing. The idea for mRNA

Figure 1.
Applications of RNA-based therapeutics in medicine that are discussed in this book.
technologies as biopharmaceuticals for infectious and oncological diseases materialized in the early twenty-first century. Two companies, BioNTech and Moderna, which were founded two years apart (in 2008 and 2010, respectively), began working on the commercialization of mRNA-based vaccines against flu and subsequently Ebola disease [2]. The COVID-19 pandemic has speeded up mRNA technologies and culminated in rapid mRNA vaccine testing and approval for use in humans. RNA-based therapeutic vaccines (e.g., those developed to fight against SARS-CoV-2 infection) have been proven to be safe and effective. Several of the vaccines were approved by the FDA and the European Commission (EC).

An interesting formulation of double-stranded RNAs is one which activates TLR-3 receptors. This drug is sold under the generic name Rintatolimod in South America and Canada. The drug is indicated for treatment of patients with chronic fatigue syndrome, a poorly understood complication of many viral infections [3]. RNA drugs have great therapeutic potential to modulate inflammatory responses and combat oxidative stress to prevent tissue and organ damage during severe infections; however, the investigations of RNA drug utility are still at the pre-clinical stage [4, 5]. Greater attention has been devoted to antiviral RNA therapeutics, several of which have progressed to clinical phases 2 and 3, including Favipiravir (against Ebola Disease) and siRNA drugs for the treatment of chronic hepatitis B and HPV virus infections [6–8]. The anti-SARS-CoV-2 RNA analogs Ledipasvir and Remdesivir have recently been granted FDA approval to treat COVID-19 infection [9–11].

RNA therapies are evolving as individualized treatment solutions for cancer. In 2006, Nobel Prize was shared by Professors A. Fire and C. Mello for their discovery of gene silencing by double-stranded RNA interference (RNAi) [1]. siRNAs (as well as miRNAs) have been tested to inhibit overexpressed genes in various malignant tumors, including multiple myeloma, pancreatic, and hepatocellular carcinomas [12]. Unfortunately, the side effects that were observed in the studies’ participants along with poor efficacy resulted in the termination of many studies.

Antisense Oligonucleotides (ASO) became the number one choice for therapeutic design in the early twenty-first century to treat cancers that resulted from oncogene duplication or overexpression (e.g., C-MYB, BCL, IGF1R) [13]. Several ASO therapeutics have been incorporated into the conventional treatment of oncological diseases, including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), and glioblastoma [14]. More recently, RNA aptamers and raptamers have been tested as multifunctional RNA drugs in the field of oncology [15]. For example, bi-specific aptamers were designed to activate receptors on tumor-infiltrating T cells against cancer-associated receptors. The aptamers linked to a siRNA against the gene of interest can downregulate the target gene directly in tumor cells or modulate tumor cell immunogenicity, thus enhancing anti-tumor immune response. Aptamers conjugated to chemotherapeutic molecules can be delivered in a cell-specific manner (e.g., if designed to bind tumor oncomarkers) [15]. Such properties significantly expand the portfolio of malignant diseases, including cancers with immunosuppressive properties.

Human trials of non-formulated mRNA- and mRNA-based dendritic-cell cancer vaccines have been taking place since the mid-2000s. Several dozens of ongoing clinical trials are well described in [16]. The majority of them is designed as study arms in combination with standard immune checkpoint therapies or individualized biologics to treat devastating cancers such as glioma, melanoma, prostate cancer, and non-small-cell lung, pancreatic, and colorectal neoplasms. The future goal is to achieve targeted delivery, attain kinetics of mRNA expression, overcome cancer mutation rate, and reduce unintended host-immune reactions [17].
siRNA drugs has become invaluable in the field of transplantology, where life-saving hematopoietic stem cell transplantation is accompanied by numerous pre- and post-transplant complications [18, 19]. One of the complications is hepatic veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS), which has been successfully treated by the drug Defibrotide, which was formulated as a mixture of single- and double-stranded oligonucleotides [20]. Patients who undergo transplantation procedures are often at high risk for GVHD and acute kidney injury, which now can be mitigated by siRNA against p53 mRNA (Teprasiran, Quark-Pharmaceuticals) [21].

Alnylam, a U.S.-based company, is pioneering siRNA treatments against rare hereditary diseases. Several siRNA drugs have already been approved by the FDA and granted orphan drug designation [22]:

- Vutrisiran and Patisiran target TTR in patients with hereditary variant transthyretin amyloidosis and hereditary TTR-mediated polyneuropathy/cardioomyopathy [23, 24];
- Inclisiran was designed to knockdown PCSK9 in patients with homozygous familial hypercholesterolemia [25];
- Lumasiran and Nedosiran were designed to knockdown HAO1 and LDHA genes, respectively, to treat primary hyperoxalurias type I–III [26, 27];
- Givosiran is a siRNA drug that targets the ALAS1 gene as a treatment for acute hepatic porphyria (AHP) [28].

Another group of rare diseases, hemophilia A and hemophilia B, are being evaluated for management with monthly subcutaneous administration of siRNA-based therapy fitusiran (Sanofi) [29]. Currently, novel siRNA drugs are entering clinical trials almost daily; information about them can be found at clinicaltrials.gov and ema.europa.eu/en/medicines. Many pre-clinical studies are in progress at academic institutions and biopharmaceutical companies [30].

S. Altman and T. Cech were awarded a Nobel prize for the discovery of catalytic RNAs, now named Ribozymes [1]. This diverse group of single-stranded RNAs acts as enzymes when folded into secondary and tertiary structures [31]. Several clinical trials investigated the utility of Ribozymes in the treatment of HIV-infected individuals [32, 33]. Therapeutic Ribozymes were designed and tested against angiogenic factor VEGF1, which is often overexpressed in cancer; however, due to higher interest in the commercialization of RNAi-based therapies, Ribozyme trials eventually stopped.

E. Charpentier and J. Doudna received the Nobel Price for the discovery of CRISPR-Cas in the middle of the COVID-19 pandemic [34]. CRISPR technology, which was initially designed to disrupt the gene of interest for experimentation, now is thought to be applied to treat inherited diseases. CRISPR-Cas is becoming a great alternative to siRNA therapeutic applications [35].

There are estimated 5000–8000 rare monogenic diseases that can be cured by gene therapies, including CRISPR-Cas [36]. Commercialization of CRISPR technology leads to several clinical trials that utilize CRISPR-Cas9 modalities to correct mutations that cause sickle cell anemia, β-thalassemia, cystic fibrosis, Duchenne muscular dystrophy, Huntington’s chorea, and hereditary retinal degenerative diseases [24, 37]. The versatility of CRISPR-Cas therapeutic applications is wide and has the potential to provide twenty-first-century cures to newborns. Additionally, it may even provide cures, preconceptionally, to families affected by the genetic disease.
3. Conclusions

This book presents distinct classes of RNA therapeutics, ranging from single-stranded antisense oligonucleotides (ASOs) and subclasses of RNA interferences (miRNAs and other RNAi) to \textit{in vitro} transcribed mRNAs and RNA vaccines. Also presented are some of the challenges in RNA drug engineering, delivery, and specificity. Additionally, the improvement of pharmacological effectiveness is discussed.

RNA therapeutics have already had a significant impact on medicine, the economy, and overall public health. They are becoming prescription drugs, and this holds great promise for modernizing healthcare [38]. National Genome Research Institute has recently launched a genotype-first approach to trace genomic variants back to human disorders. Accumulated data on human genome sequencing may inevitably lead us to a preventive medicine mindset. Monumental breakthroughs in molecular biology, computational chemistry, bioinformatics, and individualized genomics, which undoubtedly propelled RNA therapeutics through the commercialization stage, are also examined in this book.

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Conflict of interest

None declared.

Acronyms and abbreviations

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>EC</td>
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<tr>
<td>TLR-3</td>
<td>toll-like receptor</td>
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<td>CRISPR</td>
<td>clustered regularly interspaced short palindromic repeats</td>
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<td>IGF-1R</td>
<td>IGF type-1 receptor</td>
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<td>miRNA</td>
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<td>siRNA</td>
<td>small interfering RNA</td>
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<td>PCSK9</td>
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<td>GVHD</td>
<td>graft versus host disease</td>
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