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Chapter

A New Era of RNA Personalized Vaccines for Cancer and Cancer-Causing Infectious Diseases

Ana Ayala Pazzi, Puneet Vij, Nura Salhadar, Elias George and Manish K. Tripathi

Abstract

RNA vaccines for cancer and cancer-causing infectious agents are recognized as new therapeutics and are perceived as potential alternatives to conventional vaccines. Cancer is a leading cause of death worldwide, and infections (certain viruses, bacteria, and parasites) are linked to about 15–20% of cancers. Since the last decade, developments in genomics methodologies have provided a valuable tool to analyze the specific mutations, fusions, and translocations of the driver genes in specific cancer tissues. The landscape of the mutations identified by genome sequencing and data analysis can be a vital route to personalized medicine. This chapter will discuss the present state of mRNA vaccine development and ongoing clinical trials in oncology.

Keywords: mRNA, therapeutics, cancer, clinical trials, vaccine

1. Introduction

Conventional vaccine approaches were adopted for infectious diseases, but the RNA (mRNA) vaccine developed for COVID-19 changed the vaccine development landscape, providing global recognition and a new alternative. Moreover, RNA vaccines consist of rapid development, scalability, and cell-free manufacturing [1]. RNA vaccines are the clinical reality and are being studied to treat cancer, diseases like HIV, influenza, and genetic disorders [2]. mRNA cancer vaccines have received lots of attention, and efforts have resulted in some rapid developments, especially in the last 5 years [3, 4].

Cancer is not an infectious disease; vaccines for cancer aim to clear active disease instead of preventing disease, the only exception being the recently approved vaccine that prevents cancers caused by the human papillomavirus (HPV) [5]. Cancer is a particularly unpredictable disease that occurs due to random genetic events, and mutations are the driving force [6, 7]. Even though most potentially detrimental mutations are eliminated or neutral in nature, one mutation may cause a single somatic cell to develop an advantage over the rest, generating a pattern of amplified proliferation and progression that, over time, gives rise to a cancerous tumor [8]. Genome profiling provides insight into the diversity and heterogeneity within each type of cancer, which is a significant challenge in finding the right therapy for each patient [9, 10].

1.1 What is mRNA?

Messenger RNA is a versatile, single-stranded molecule that mediates protein translation, posttranscriptionally regulates genes, and has other regulatory properties inside the cell [11, 12]. A mature mRNA will have a protein-encoding region, or open reading frame (ORF), between a start and a stop codon enclosed in a single strand with a 7-methyl-guanosine and untranslated region at the 5′ end and a poly-A tail with its respective untranslated region at the 3′ end. Both the 5′ cap and the poly-A tail are essential for mRNA maturation and stability, therefore heavily regulating the efficiency of protein translation and mRNA degradation [13, 14]. Generally, once the mRNA enters the cell, it has a short time to produce the protein it is encoding for before it starts to degrade [15]. This is a challenge when studying mRNA as a therapeutic delivery, especially in hereditary diseases [16, 17].

1.2 RNA therapeutics

mRNA presents a viable option for patient therapeutics comparable to existing cancer therapies [13, 18]. Since the inception of RNA-based cancer vaccination, many preclinical and clinical studies have explored the idea of mRNA-based anticancer vaccines using autologous RNA-transfected dendritic cells or direct injection into the organism. For instance, mRNA acts outside the cell nucleus, eliminating the need to bypass this membrane while still being a messenger for genetic information. In the cytoplasm, the exogenously delivered mRNA starts protein translation, whereas DNA must reach the nucleus first and then be transcribed into mRNA to produce an effect in the cell [15 19, 20]. Additionally, mRNA does not incorporate into the genome; instead, it produces proteins for a short period, significantly minimizing the risk of mutations in the patient and long-term side effects [21]. Moreover, mRNA drugs can be manufactured relatively inexpensively to express any protein for virtually any disease. Multiple research studies conducted during the past few decades have demonstrated the curative properties of this technology and its ability to target various health conditions [22–25]. This is particularlytrue in the case of synthetic mRNA-based vaccines that were developed rapidly
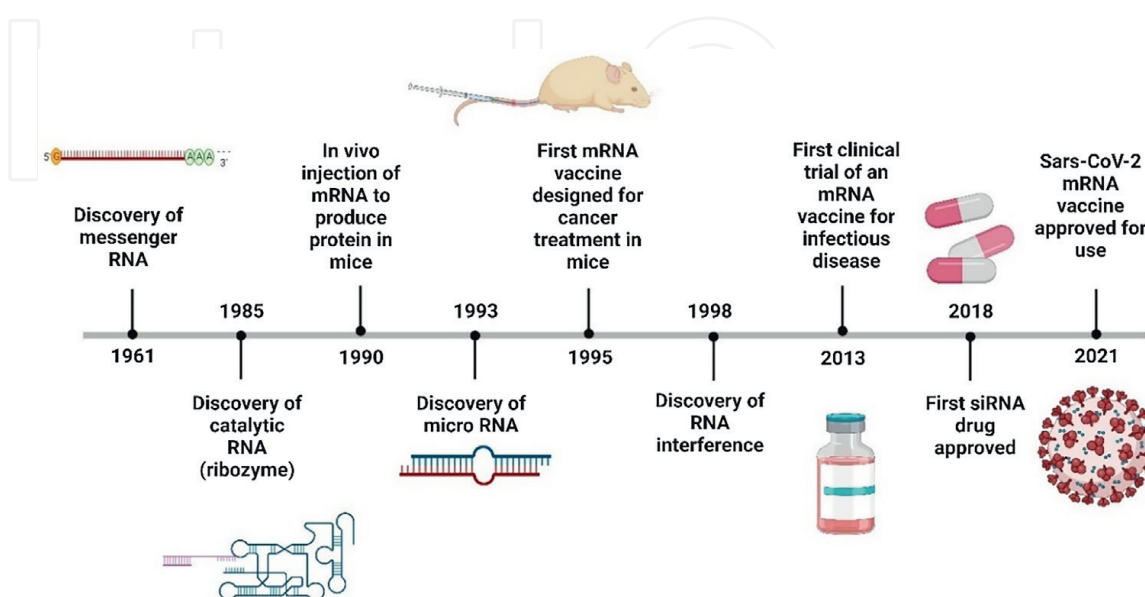

Figure 1.
Key discoveries and advances in mRNA-based therapeutics. Created with BioRender.com.

during the COVID-19 pandemic, and many years of research in RNA biology paved the way for this unparalleled achievement. The first mRNA vaccine approved for emergency use for infectious disease (COVID-19) by the FDA was created by BioNTech and Pfizer [26]. The candidates for the vaccine (BNT162b1 and BNT162B2) were initially identified in Germany and were further studied in the United States [27]. These targets were chosen as they encoded the spike protein of the SARS-CoV-2 virus. The delivery method for this vaccine consisted of lipid nanoparticles [28]. The Moderna vaccine also targeted a similar gene product and was delivered intramuscularly to the patient. **Figure 1** shows the history of RNA and the recent development of mRNA-based COVID-19 vaccines.

2. Challenges and advantages of mRNA vaccines

The delivery of mRNA into a cell is particularly challenging due to the size of 300 to 5000 bp, in contrast to microRNA and silencing RNA, which only go up to 5–15 bp in size. Additionally, instability due to charges in the molecule is another factor that impairs its functionality as a therapy, as it cannot penetrate the cell membrane. However, some cells can uptake naked mRNA, a relatively inefficient process, because most cells have a low rate of mRNA uptake [29, 30]. In contrast, the immature dendritic cell is an exception, which can take up mRNA through the macro pinocytosis pathway and accumulate mRNA efficiently [15].

One advantage of mRNA vaccines is a simplified development process, which only requires a few laboratory techniques and resources. In contrast, the production of biologics such as plasmid DNA vaccines can be time-consuming and expensive compared to mRNA vaccines, thereby augmenting the interest in mRNA therapeutics. However, in the initial stages of the study surrounding mRNA vaccines, researchers struggled to stabilize the product and increase its safety profile [31, 32]. Some solutions to these issues included chemical modification of mRNA sequences (e.g., via nucleoside manipulations) and packaging into nanocarriers [33, 34]. RNA-active vaccines (protamine-formulated mRNA vaccines) encoding six prostate cancer-specific antigens (CV9104) and five non-small cell lung cancer (NSCLC) tumor-associated antigens (CV9201) have been investigated clinically for safety, overall survival, and progression-free survival [35].

The challenges that must be overcome in the production of mRNA vaccines include the negative charge of the RNA (which must cross the hydrophobic cell membrane) and the strong immune reaction of exogenous RNA, which can cause cell toxicity [29, 36]. Recent research has overcome these obstacles by personalization of vaccines for their ability to target specific diseases [16, 37]. Moreover, once synthetic mRNA is translated into protein in the cytoplasm, it is subsequently degraded within a few minutes or hours, thereby preventing any harmful effects.

Various forms of mRNA therapy include replacement therapy (to synthesize a defective protein), vaccination, and cell therapy (which entails ex vivo transfection) [16]. Another challenge is that antigen presentation is often short-lived, as mRNA can be degraded by exogenous RNases [21]. However, this can be addressed using self-amplifying RNA sequences utilized by alphaviruses, which prolong antigen expression [38].

3. Immunology of vaccination

The human immune system is comprised of innate and adaptive immune cells that play unique roles in eliminating a pathogen. The innate immune system serves as a

first-line response to a pathogen and acts via lysis or phagocytosis [39, 40]. Since it is possible for pathogens to evade this first-line defense, the adaptive immune system can prompt the activation of humoral and cell-mediated immunity (see **Table 1**) [33, 41]. Humoral immunity consists of B-cells that produce antibodies, which can eliminate a pathogen via various mechanisms. Antibodies may envelop the pathogen with their Fc (constant fragment) portions which are subsequently recognized by phagocytic cells [42]. Other mechanisms include the creation of immune complexes which trigger the complement cascade, expressing receptors on phagocytic cells and directly attaching antibodies to viruses via receptor binding sites [33]. Cell-mediated

Immune response	Immune product	Infectious agents
Humoral	Immunoglobulin G	Bacteria and viruses
	Immunoglobulin A	Microorganisms
	Immunoglobulin M	Bacteria
	Immunoglobulin E	Parasites
Cell-mediated	Cytotoxic T-lymphocyte	Viruses, mycobacteria, parasites
	T-helper cells 1	Mycobacteria, fungi

Table 1.
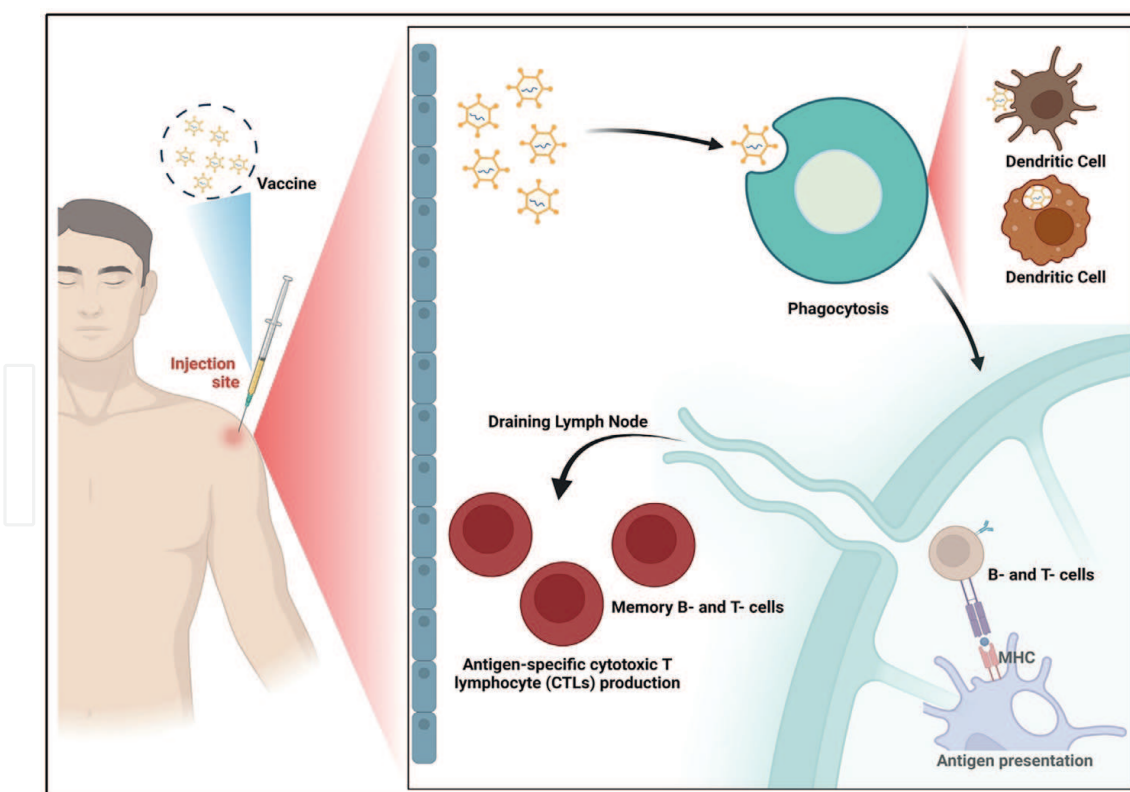*Immune response, products, and associated infectious diseases [33].*

Figure 2.
Administration of vaccine leading to immunity production steps. Macrophages and dendritic cells are phagocytic antigen-presenting cells (APCs). Upon vaccine administration, these APCs take up the contents of the vaccine. After activation of APCs by specific antigens, the migration occurs toward lymph nodes (LNs) as shown. Within the LNs, the antigen is presented to lymphocytes for further activation. Antigen-specific B- and T-cells then multiply clonally to create their progenitors by recognizing the same antigen. Long-term protection is also achieved by the production of memory B- and T-cells against pathogen infection. Created with BioRender.com.

immunity clears infected cells via cytotoxic T-cells and T-helper cells. The B- and T-cells of the adaptive immune system are more specific to the pathogen, and vaccines seek to build up this response to evade the severe consequences of infection. Upon infection, the innate immune system prompts B-cells and T-cells (specific to the virus) increase in number, thereby strengthening their degree of protection [33, 43]. The vaccine entry requires uptake *via* antigen-presenting cells, which deliver the vaccine to secondary lymphoid organs where T- and B-cells are produced (see **Figure 2**).

Once the infection has cleared, some of the B- and T-cells will undergo apoptosis, but some may persist and will be able to respond if re-infection of the same pathogen
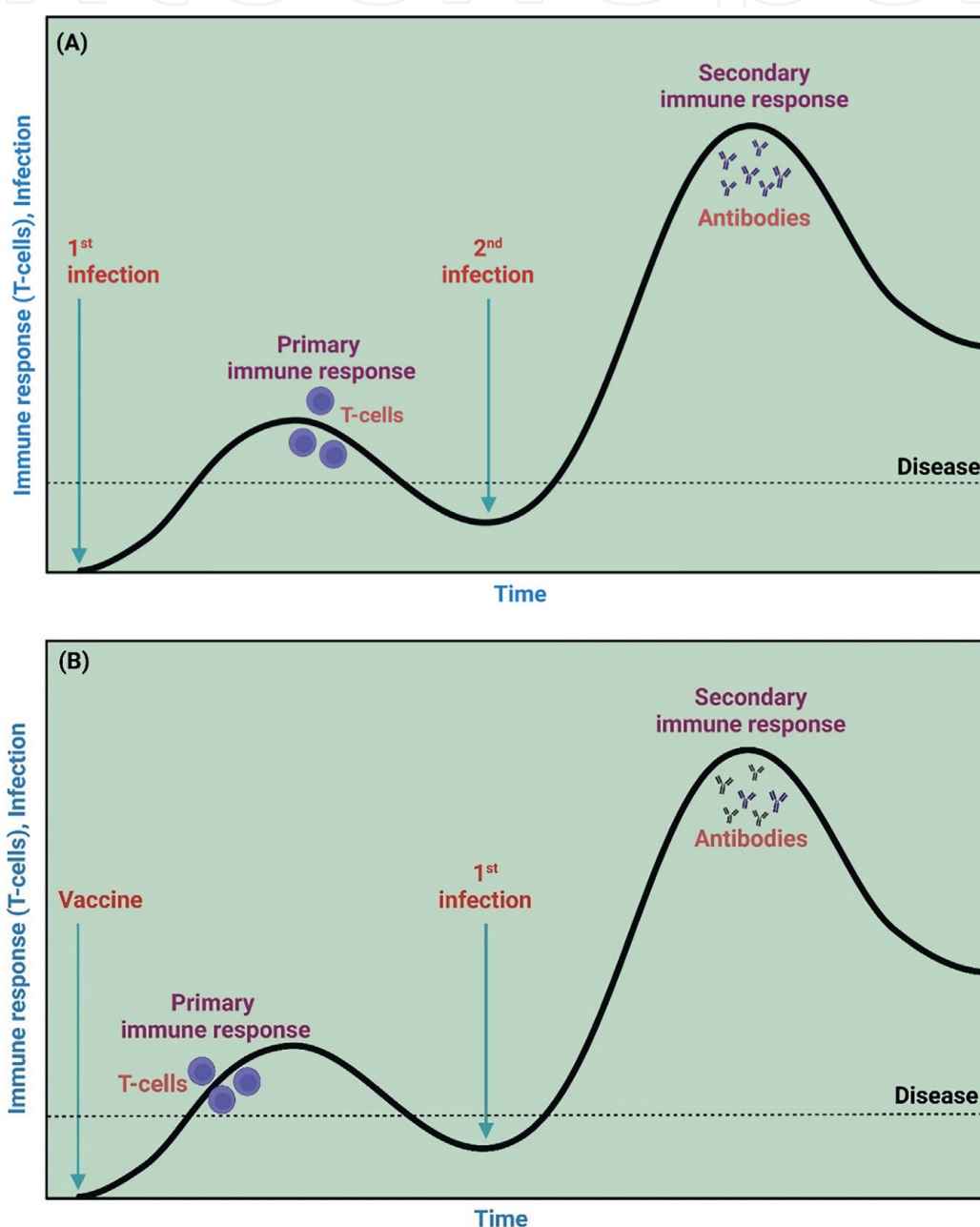

Figure 3.
Adaptive immune responses after two different scenarios: (A) infection: This part of the figure represents the response after primary and secondary infection. The primary infection causes disease manifestation, as there is a lag in developing T- and B-cells. The secondary infection causes the memory T-cells to respond quickly and helps develop antibodies to fight the infection or pathogen. (B) Administration of vaccination follows a similar pattern without the manifestation of the disease. Created with BioRender.com.

occurs (see **Figure 3**). Thus, the aim of achieving a faster immunological response to a pathogen is achieved through this mechanism [44].

For effective antibody production, the coordinated actions of CD4-positive follicular helper T-cells and B-cells depend on the successful presentation of a protein antigen, which is recognized by its specific B-cell clone in secondary lymphoid organs such as the lymph node and provides the first signal for B-cell activation [45]. This specific B-cell clone processes an extracellular protein antigen by uptake into endosomes and lysosomes for proteolytic digestion into peptides of varying length for incorporation into highly diverse HLA Class II molecules, which are imported from the endoplasmic reticulum [46] and can bind antigenic peptides of 10 to 30 residues in length. The mature HLA Class II molecule bearing its antigenic peptide is then expressed on the surface of the B-cell for presentation to CD4-positive follicular helper T-cells at the periphery of the follicles of secondary lymphoid organs. The interaction between the antigen-presenting B-cell and the follicular T-cell depends on specific recognition of the mature HLA Class II molecule containing its peptide antigen by its T-cell receptor. It provides a second signal for the activation of the B lymphocyte resulting in its proliferation and differentiation into antibody-secreting plasma cells and memory B-cells [47], with the latter capable of rapid response to a second exposure to its specific antigen resulting in antibodies of higher affinity.

Cell-mediated immunity targets cells functioning as reservoirs of infection or displaying foreign peptides. The mechanism of antigen presentation is analogous to the Class II pathway described above but differs in several ways. First, the protein antigen is present in the cytoplasm, which is processed by ubiquitin-mediated proteasomal digestion resulting in small peptide fragments about nine residues in length that are then imported into the endoplasmic reticulum. Here, they may bind to HLA Class I molecules if the fragments contain sufficient antigenicity. The mature HLA Class I molecules with their bound antigenic peptides are then displayed on the antigen-presenting cell surface for recognition by an activated CD8-positive cytotoxic T cell specific for this complex [48, 49]. Delivery of the cytotoxic payload of this effector T-cell results in the activation of the apoptotic pathway of the target cell and its elimination.

A second exposure to an antigen, such as a booster, is often required for a more robust and effective immune response. Thus, a successful vaccine design strategy requires this immunologic knowledge and characteristics of its protein target, where computational methods to determine peptide antigenicity among the highly polymorphic HLA molecules are helpful [50, 51].

4. Clinical development of mRNA vaccines for the prevention of cancer-causing infectious diseases and as cancer therapeutics

4.1 mRNA vaccines for the prevention of cancer-causing infectious diseases

Microbial infection accounts for around 15% of all human cancers, totaling approximately two million yearly cases [52]. Bacterium Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein–Barr virus (EBV) are primarily responsible for 97% of these cancers [53]. Besides cancer-causing infectious diseases, mRNA vaccines are also being studied as a preventive treatment against influenza A, zika, cytomegalovirus, respiratory syncytial, and rabies [16].

Currently, mRNA vaccines have been designed for two of seven viruses that can cause cancer (oncoviruses). One of the examples is the liposome-encapsulated mRNA vaccine for human papillomavirus type 16 (HPV-16). It encodes for the oncoproteins E6 and E7, which have the potential for immunomodulation and antineoplastic activities [54]. Upon intravenous administration, the liposomes protect the RNA degradation within the bloodstream leading to uptake by APCs [55]. Translocation to the cytoplasm leads to the translation of E6 and E7 oncoproteins. After the processing of the proteins, the peptide complexes are presented to the immune system and hence induce antigen-specific T-cell responses (CD8+ and CD4+) against HPV16 E6 and E7 [56]. The associated clinical trial is mentioned in **Table 2**. Another example is mRNA-1189 Epstein–Barr virus (EBV) vaccine. This encodes EBV's envelope glycoproteins (gH, gL, gp42, and gp220), which mediate viral entry into B-cells and epithelial surface cells, the primary targets of EBV infection [57, 58]. The viral proteins in mRNA-1189 are expressed in their native membrane-bound form for recognition by the human immune system.

Brand	Title	Conditions	Phase
BNT111	Trial with BNT111 and Cemiplimab as a single agent and/or in combination	Melanoma stage III/ and/or IV	Phase II
BNT112	Prostate Cancer Messenger RNA Immunotherapy	Prostate cancer	Phase I and II
BNT113	Safety, tolerability, and therapeutic effects of bnt113 in combination with Pembrolizumab/ Alone for participants with head/neck cancer positive for HPV16 and PD-L1 expression	Head and neck cancer	Phase II
BNT116	Clinical trial evaluating the safety, tolerability, and preliminary efficacy of BNT116 alone and/ or in combination	Non-small cell lung cancer	Phase I
BNT122	Comparing the efficacy of RO7198457 Vs. Watchful waiting in patients with high-risk stage II and Stage III colorectal cancer	Colorectal cancer Stage II/III	Phase II
RO7198457	A study of RO7198457 as a single agent and/or in combination with atezolizumab in participants with advanced or metastatic tumors	Melanoma Bladder cancer	Phase I
RO7198457	A study of the efficacy and safety of RO7198457 in combination with atezolizumab Vs. Atezolizumab alone	Non-small cell lung cancer	Phase II
RO7198457	A study to evaluate the efficacy and safety of RO7198457 in combination with pembrolizumab Vs. pembrolizumab alone in participants with previously untreated advanced melanoma	Advanced melanoma	Phase II
mRNA-4157	Safety, tolerability, and immunogenicity of mRNA-4157 alone in participants with resected solid tumors and/or in combination with pembrolizumab in participants with unresectable solid tumors	Solid tumors	Phase I
	An efficacy study of adjuvant treatment with the personalized cancer vaccine mRNA-4157 and pembrolizumab in participants with high-risk Melanoma	Melanoma	Phase II

Brand	Title	Conditions	Phase
mRNA5671/ V941	A study of mRNA-5671/V941 as monotherapy and in combination with pembrolizumab	Non-small cell lung cancer Pancreatic and colorectal Neoplasms	Phase I
mRNA-2752	Dose escalation study of mRNA-2752 for intra-tumoral injection to participants with advanced malignancies	Relapsed/ refractory solid Tumor malignancies or lymphoma	Phase I
SW1115C3	A study of neoantigen mRNA personalized cancer in patients with advanced solid tumors	Solid tumor	Phase I
mRNA-4539	Study of mRNA-4359 administered alone and in combination with Immune Checkpoint Blockade in participants with Advanced Solids Tumors	Advanced solid tumors	Phase I and II
BNT 141	Safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy trial of BNT141 in patients with unresectable CLDN18.2-positive gastric, pancreatic, ovarian, and Biliary tract tumors	Solid tumor Gastric, pancreatic, biliary tract, and metastatic cancer	Phase I and IIa

Table 2.
Clinical trials of mRNA encoding TAAs and TSAs (clinical trials.gov).

Kaposi's sarcoma-associated herpesvirus (KSHV) is the cause of three human malignancies: Kaposi's sarcoma, primary effusion lymphoma, and the plasma cell variant of multicentric Castleman disease. Currently, there are no well-developed KSHV vaccine candidates. One of the clinical trials completed in 2019 looked at the impact of Valganciclovir on severe immune reconstitution syndrome (S-IRIS)-Kaposi Sarcoma (KS) mortality: an open-label, parallel, randomized controlled trial, in which 40 patients were randomized and 37 completed the study. It was concluded that Valganciclovir significantly reduced the episodes of S-IRIS-KS. Although attributable KS mortality was lower in the experimental group, the difference was insignificant. Mortality was significantly lower in EG patients with pulmonary KS [59].

4.2 Development of mRNA vaccines as cancer therapeutics

Several widely used conventional cancer therapies, such as chemotherapy and hormone therapy, have proven effective in treating cancer [60]. Chemotherapy involves a series of drugs that impair DNA synthesis, thus fatally interrupting the physiological processes of cancerous and healthy cells [61, 62]. However, the success rates for this treatment are most effective only in highly proliferative and low heterogeneity cancers. Alternatively, hormonal or endocrine therapy targets growth signaling pathways by interfering with hormone receptors in cancer cells [63]. Thus, it is suitable for low-proliferating cancers such as breast and prostate [64].

Among immunotherapeutic treatments, mRNA vaccines stand out due to their superior specificity and potential for adaptability according to the genetic profile of each patient's cancer. To produce an efficient, individualized cancer vaccine, specific genetic mutations in the cancerous cells are identified to produce neoantigens that

could bind to T-cells and elicit an immune response in the patient more specifically than traditional systemic and local methods [37]. However, this treatment has faced challenges, such as a need to enhance the identification of potential genetic markers that could provide the specificity needed for cancer vaccines [23, 65].

RNA vaccines targeting various cancers are in the development and undergoing clinical trials. Examples of RNA cancer vaccines include CV9202 (CureVac), which targets multiple antigens found in non-small cell lung cancer [13]. Moderna is also developing an mRNA vaccine that targets the K-RAS proto-oncogene that plays a role in the pathogenesis of non-small cell lung cancer, colorectal cancer, and pancreatic adenocarcinoma [66]. The mRNA-4157 against melanoma, created by Moderna, and the BNT122 vaccine against prostate cancer, created by BioNTech, targets various solid tumors and are individualized vaccines [35, 67]. These specific vaccines are designed to elicit the immune response toward tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) in malignant tumor cells. These vaccines used next-generation sequencing technology to identify and isolate antigen epitopes unique to each patient, creating a more refined vaccine. Various clinical trials exist for different cancer vaccines (see **Table 2**) [2]. TAAs are present in both normal tissues and tumors, as these are non-mutated self-antigens. For a few tumors, TAAs are desirable vaccine targets. However, immune tolerance responses, such as central and peripheral, may be triggered by vaccines that can express TAAs and can reduce clinical vaccination efficacy [68]. Therefore, these kinds of vaccines are still in a phase where they are used in combination with immune checkpoint inhibitors [69]. With many ongoing clinical trials in different phases and preexisting clinical information or data, personalized vaccines can potentially be effective in cancer treatment. BioNTech vaccine BNT122 RO7198457) and Moderna vaccine mRNA-4157 are two personalized mRNA-based cancer vaccines in phase II clinical trials.

There is a significant increase in ongoing or completed studies/clinical trials in mRNA vaccines. In addition, various other clinical trials evaluate the tolerability, safety, immunogenicity, and/or efficacy of mRNA-personalized vaccines in participants with tumors. In this way, we are stepping into a new era of therapeutic mRNA-based cancer vaccines or prevention and treatment of currently incurable malignant diseases.

5. Summary

This chapter describes the technology, the basics of the immune response, and examples of developing mRNA vaccines for cancer and cancer-causing infectious agents. They can be used for preventive and therapeutic purposes. This information is of value to interdisciplinary researchers, engineers, and healthcare professionals as it may impact the prospects of medical care. Built on the highly fueled interest and potential, we have complete confidence to predict an accelerated pace in mRNA therapy studies and development in the next decade, possibly providing many solutions for the prevention and treatment of currently incurable diseases.

Conflict of interest

The authors declare no conflict of interest.

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