Perspective



# **Messenger ribonucleic acids (mRNA) technology for future applications in cancer treatment**

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**Abstract:** Technological developments in medicine have made it possible to treat certain diseases, such as cancer, at the root level of transcription and translation with recent development in clinical pharmacology and therapeutics. The world has learned about messenger ribonucleic acids (mRNA) technology in the last two years. In that time, it has shown how quickly it can respond to situations and has almost limitless potential for future applications in the treatment of cancer. The genetic instructions or recipes that guide cells on how to use their own machinery to build proteins are carried by a molecule called mRNA. Lipid nanoparticles, an increasingly common means of delivering genes that can contain both proteins and nucleic acids, enclose the mRNA in a protective bubble that allows it to circulate freely throughout the cells. Once inside, human cells use the mRNA as a set of instructions to produce proteins that attach to the unique areas of the pathogen, or antigens. The immune system promptly produces antibodies and T-cells as defenses when it perceives foreign antigens as invaders, fortifying the system's defenses against subsequent attacks. As a result, if and when the real virus manifests, the body might be able to recognize the warning signal it sends out to help guard against infection and illness. The study demonstrated how mRNA can be a powerful tool for developing vaccines and diseases treatments, allowing human cells to put forth a lot of effort in generating proteins that trigger an immune response that defends against illnesses and preserves human organs, which marks a significant milestone in science and demonstrates the adaptability and versatility of mRNA technology for known and unknown diseases treatments.

**Keywords:** Cancer treatment, mRNA technology, DNA, Vaccines, Antibodies, COVID-19

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### **Introduction**

 The single-stranded molecule that contains the instructions needed to build proteins is called messenger ribonucleic acid, or mRNA [1]. It is a component of all living cells and plays a basic and vital role in functioning of cells in the human body. As mRNA transfers genetic information from deoxyribonucleic acid (DNA) to ribosomes that produce proteins, it is a crucial part of the process of protein synthesis in cells [2]. The mRNA is created during transcription by generating a ribonucleic acid (RNA) molecule using a section of DNA as the nucleotide sequence of the RNA chain. The nucleotides that make up this single-stranded molecule are adenine, cytosine, guanine and uracil [3]. For the reason that the sequence of nucleotides in mRNA helps determine the amino acid sequence of a protein, mRNA is essential for gene expression. The development of novel cancer medications and vaccines greatly benefits from the use of mRNA [4]. In recent times, vaccines such as the COVID-19 vaccines from Pfizer-BioNTech and Moderna have been produced with mRNA [5]. In addition to the treatment of COVID-19, mRNA technology is also very promising for the treatment of cancer, infectious diseases, and congenital genetic abnormalities [6]. mRNA was discovered in the 1960s. Due to its potential to be used in the prevention and treatment of a wide range of diseases, scientists have been researching mRNA for decades since then. After decades of ongoing research, improvements, and technological advances on mRNA, a great deal of progress was made in the early 2000s. Thanks to the pioneering work of Pieter Cullis, lipid nanoparticles have been developed as delivery vehicles for vaccines and medicines, which has been crucial for advancing mRNA technology [7].

 The recipes or instructions that tell cells how to use their own resources to make proteins are encoded in a molecule called mRNA [8]. The fragile mRNA strands are coated with PEGylated lipid nanoparticles, which act as a delivery vehicle for the RNA vaccine, allowing the mRNA to more easily pass through cells and travel through a protective bubble known as a lipid nanoparticle [9]. After entering the body, human cells use the mRNA as a set of instructions to produce proteins that attach to antigens, which are specific regions of the pathogen [10]. The foreign antigens are perceived by the immune system as intruders, which triggers the mobilization of antibodies and T-cells as defense mechanisms and prepares the body for any future attacks. Therefore, in the event that the real virus shows up, the body can identify it and raise the alarm to prevent infection [11]. At the University of Pennsylvania, research collaborators Katalin Karikó and Drew Weissman succeeded in modifying the mRNA so that it could enter cells without inducing an immune response [12]. The first mRNA vaccines for COVID-19 were developed and approved in 2020. This accomplishment furthered scientific progress that confirmed the technology's potential for future clinical innovation [13]. Humans cannot survive without either DNA or mRNA, two fundamental and important molecules in biology that are responsible for the activities of cells and immune system [14]. The human body depends on both DNA and mRNA to function and remain in balance, with each performing distinct yet separate functions. All genetic information found in the human body is stored in DNA. The mRNA, which functions like a blueprint or set of instructions, contains genetic information that is subsequently translated into enzymatic proteins, working with substrate molecules to stabilize the transition state and thereby lowering the activation energy required for a chemical reaction to occur [15]. Proteins fulfil a variety of vital functions in the human body, and mRNA directs body's cells to produce particular proteins that carry the information from the DNA from the cell nucleus into the cytoplasm [16]. The mRNA in effect takes advantage of biological processes in the human body to potentially treat and prevent diseases. Nucleoside-modified messenger RNA, or modRNA for short, is a term used to describe how some of the essential biological molecules that make up DNA and RNA are substituted with modified nucleosides during the synthesis of the RNA employed in the vaccine platform in order to improve immune evasion and protein synthesis [17]. Human cells are instructed by modRNA to produce certain proteins, which assists the body's immune system to recognize and target proteins or mutations found on certain cancer cells [18].

 Even though mRNA vaccines function differently from other vaccinations in that they do not contain the diseasecausing virus, they nonetheless boost the immune system of the body [19]. The guidelines instruct the cells of the human body how to synthesize a portion of a protein from a virus, such as the one that causes COVID-19 and the growth of cancer cells [20]. To produce the protein, which is completely safe for the body, the human cells use this protocol. The protein is recognized by the immune system of the body, which determines it as foreign material. As a result, it produces antibodies that eliminate foreign substances known as infections [21, 22]. The antibodies of the body system re-identify the virus and the malignant cells, launch an attack and eliminate them if a human comes into contact with them. The neoantigens from the patient's resected tumor are utilized to produce a customized mRNA vaccine that is used as a therapy for patients who have already been diagnosed with cancer. Vaccines against infectious diseases are not the same as cancer vaccines, which have been researched for decades. They teach the immune system to look for particular proteins, called cancer-associated antigens, which are only found in cancer cells. These mRNA vaccines are fascinating because they target specific cancer cells without harming any other healthy cells [23]. This leads to a highly customized and individualized approach and also makes the therapy a little more bearable. Although COVID-19 has made many people aware of mRNA

vaccinations, mRNA technology was initially developed to combat cancer [24]. After years of inconsistent results, scientists have finally made progress in getting the immune system to recognize and eliminate cancer cells at the earliest stages of development. A desired result, such as gene knockdown or the induced expression of a particular target protein, can be achieved by using mRNA [25]. Various techniques have been developed to achieve intracellular delivery by encapsulating or stabilizing different nucleic acid structures. The authors of this research focused on current advancements in cancer treatment and investigated various therapeutic applications of mRNA targeted at specific diseases and target tissues. As a result of the quick worldwide response to the COVID-19 outbreak [26], nucleic acidderived medicines are becoming more well-known to the public. The long-standing interest and advancements of the broad scientific community served as the foundation for the transfer of this technology, despite the apparent rapid industrial development of these mRNA vaccines. The ability to harness the intracellular machinery that underpins the fundamental principles of biology has been recognized by researchers as having enormous therapeutic potential [27]. To achieve this objective, nucleic acidbased treatments present a chance to target a variety of diseases at the transcriptional and translational levels. This tactic significantly expands the toolkit of contemporary medicine, enabling it to treat conditions that were previously thought to be incurable or to have no available treatments.

 Research and development of mRNA vaccines has been ongoing globally for some time, and the current COVID-19 pandemic and other emerging diseases have prompted the urgent need for rapid vaccine development [28]. However, there are still gaps in our knowledge about the mode of action of mRNA vaccines and their long-term performance in regards to things like safety and efficacy. This study explores the present state of vaccine development, the technology and procedures utilized to produce mRNA preventive vaccines, and the immunological responses that mRNA vaccines elicit. Important topics pertaining to the regulatory viewpoints on the assessment of mRNA vaccines are also covered.

# **Messenger ribonucleic acid mRNA structure**

 With reference to Figure 1, phosphodiester bonds that link the nucleotides together, mRNA is a single-stranded molecule [29]. Each nucleotide consists of a ribose sugar, a phosphate group and a nitrogenous base, such as uracil, adenine, guanine and cytosine are the nitrogenous bases, where DNA's thymine is replaced with uracil in this sequence [30]. Multiple critical components of the mRNA structure control the expression of certain genes coding area, the three prime untranslated region (3′-UTR) and the 5' untranslated region (5' UTR). The 5'- and 3'-UTRs are mRNA regions that control crucial post-transcriptional gene regulation processes. As regions that are transcribed but seldom translated, the 5'- and 3'-UTRs contain a myriad of regulatory elements involved in pre-mRNA processing, mRNA stability and translation initiation [31]. In the beginning, the 5'-UTR of mRNA molecule is where the sequence required to initiate translation. At the end of the mRNA molecule, the 3'-UTR contains sequences that aid in controlling translation termination and mRNA stability [32].



**Figure 1.** Structure of mRNA

 This section of DNA is responsible for translating a sequence into a protein. The production of proteins requires stability, which is ensured by the structure of mRNA. But it is crucial to understand its purposes and consider how it fits into biopharma. mRNA is a form of RNA molecule that is essential for the process of translation, which is also known as protein synthesis. mRNA transports genetic information from DNA to ribosomes, which construct amino acid sequences in proteins by using ribosomes as a template [33], representing a few of the primary roles of mRNA. Due to its length and structural properties, mRNA is produced and characterized differently than other RNA therapies, such as small-interfering RNA (siRNA), which is made up of short double-stranded RNA (dsRNA). In vitro transcription (IVT), which uses linearized DNA as a template, an RNA polymerase and nucleotide triphosphates in a buffered environment, is now being used to produce mRNA [34].

 In the end, the refined IVT mRNA is similar to fully developed, mature endogenous mRNA molecules found in the cytoplasm of eukaryotic cells [35]. Different methods of mRNA chemistry and production have been developed to control innate immune responses, because mRNA and some IVT byproducts are intrinsically immunostimulatory [36]. While mRNA vaccines also employ genetic materials

that express antigen proteins, they differ from other genetic material-based vaccines in a number of ways. When mRNA vaccines are administered directly into the cytoplasm of cells, they can express antigen proteins, but DNA vaccines require cellular entry into the nucleus in order to express encoded proteins. This distinction allows mRNA vaccines to express the target proteins with a high translation efficiency and at a considerably higher rate than DNA vaccines. Since RNA cannot be inserted into the host genome, there is no possibility to generate insertional mutagenesis. Using a cell-free technology, the mRNA vaccines may be produced quickly, extensively, and affordably.

### **Protein synthesis**

 The diagram of the protein synthesis process displays an mRNA and a ribosome. The process of translating DNA into mRNA in the cell nucleus, the processing of the mRNA and its export into the cytoplasm is depicted in a diagram of protein synthesis. There, ribosomes bind to the mRNA to aid in translation, while transfer RNA (tRNA) molecules carry the amino acids that correspond to the mRNA codons [37]. The Figure 2 readily enables scholars to understand this process by recognizing the class 12 protein synthesis diagram. Transcriptional and translational processes lead to the phases of protein synthesis that are necessary for cellular activity. The intricate procedure converts genetic data into proteins that are essential for the functions of life. A step-by-step process of translating genetic information encoded in DNA into mRNA and then into proteins is depicted in the protein synthesis diagram. The stages of protein synthesis are depicted in the accompanying well-labeled diagram in Figure 2.



**Figure 2.** Diagram of protein synthesis to release mRNA into the cytoplasm [38].

 **Transcription:** The nucleus of the cell is where transcription begins, as mRNA is synthesized using DNA as a template [39]. In order to unwind and separate the DNA strands, the enzyme RNA polymerase attaches itself to the promoter region of an i.gene on the DNA molecule. RNA polymerase creates a complementary mRNA molecule by adding nucleotides in accordance with the base-pairing rules (A-U and G-C) and using one of the strands as a template [40]. After transcription is finished, the mRNA transcript separates from the DNA and goes through processing, which includes removing introns (non-coding sections) and adding a 5′ cap and a poly-A tail (polyadenylation) [38]. Subsequently, the mature mRNA molecule leaves the nucleus and moves into the cytoplasm, the mRNA's codons come into contact with the active

site of the ribosome, causing the nucleotide sequence of the mRNA to be translated into an amino acid sequence [41]. This is accomplished by using tRNAs as adaptors, which add each amino acid to the end of the expanding polypeptide chain in the correct order (see Figure 2).

 Refer to Figure 3 above, pseudouridylation is a posttranscriptional isomerization reaction that converts a uridine into a pseudouridine (Ψ) within an RNA chain. Ψ has chemical properties that are distinct from those of uridine and any other known nucleotides [42]. The experimental data collected thus far have indicated that Ψ is present in many different types of RNAs, including coding and noncoding RNAs. Ψ is particularly concentrated in rRNA and spliceosomal snRNAs and plays an important role in protein translation and splicing of pre-mRNA, respectively.

Translation: The process of translating an mRNA sequence into a polypeptide chain, or protein, takes place in the cytoplasm. When the mRNA binds to a ribosome, the process starts. The three essential phases of translation are initiation, elongation and termination, as illustrated in the figure of protein synthesis. During initiation, the initiator tRNA, which carries the amino acid methionine, attaches to the start codon (AUG) of the mRNA, while the small ribosomal subunit connects to the mRNA molecule [43]. After that, the big ribosomal subunit unites to produce a functional ribosome. As the ribosome elongates the mRNA molecule, it reads the codons one after the other in a sequential procedure. A tRNA molecule containing the complementary anticodon and the corresponding amino acid attaches to the mRNA codon by base pairing. Each codon represents a specific amino acid. A polypeptide chain grows as a result of the ribosome's catalysis of the process of peptide binding between neighboring amino acids.

 Pseudouridylation can be catalyzed by two different mechanisms, namely an RNA-independent mechanism and an RNA-dependent mechanism [44]. While the RNA-independent mechanism can be observed across species from bacteria to humans, the RNA-dependent mechanism is unique to eukaryotes and archaea. The recent development of pseudouridine-seq techniques has led to the identification of a number of new Ψs in various types of RNA, including mRNA. This offers a great opportunity to develop new, better methods or to further perfect existing technologies. The identification of new Ψs in mRNA has opened the door to further experiments directed towards understanding the function of mRNA pseudouridylation  $[42]$ 

 **Termination:** The mRNA is terminated when it encounters one of the stop codons (UAA, UAG or UGA), which act as signals on the mRNA to stop protein synthesis [32]. When protein synthesis is complete, the ribosome releases the finished polypeptide chain. The recently produced protein could go through additional folding and changes before reaching its functional shape.



**Figure 3.** Post-transcriptional pseudouridylation in mRNA as well as in some major types of noncoding RNAs [42].

# **mRNA potential for cancer vaccines and treatment**

 The study of developments in mRNA cancer vaccines from various aspects, such as antigen and target expression and selection, vector and adjuvant use, delivery methods and preclinical testing, has been established [38]. The treatment for cancer appears to be another area where mRNA technology has potential. The use of mRNA to trigger an immune response against cancer cells is being investigated by researchers in the current work. mRNA has the ability to encode particular proteins that are expressed by cancer cells and can be utilized to initiate an immune response aimed at eliminating the cancer cells [38]. The adaptability of vaccines based on mRNA is another benefit. Through mRNA sequence modification, the same approach can be applied to target distinct viruses or cancer cells. This implies that a variety of diseases could benefit from the quick development and application of mRNA-based vaccines.

 Figure 4 summarizes the mechanism underlying the development and function of antitumor T lymphocytes, which are the key anticipated effector cells mediating

the therapeutic benefits of these vaccines. At the site of vaccination, DCs absorb mRNA, which they then translate, process and display on the cell surface as antigen- histocompatibility complex (MHC I/II) multiuse building [45]. The activation and proliferation of T cells result from activated DCs' presentation of antigen-MHC I/II complexes to the T cell receptor (TCR) on the surface of CD8+/CD4+ T cells, which is the initial signal of lymph nodes. Costimulatory signaling molecules such as (CD80/CD86, OX40 ligand (OX40L)) binding to the receptors CD28, OX40 on the T cells (the second signal) and cytokines (interferon (IFN) I, interleukin 12 (IL-12), IL-1) binding to cytokine receptors on the T cells (the third signal), cooperate to further facilitate this process [46]. Furthermore, IL-2 secreted by CD4+ T cells can promote

the proliferation of CD8+ T cells [47]. Under the influence of chemokines such as CC-chemokine receptor 7, CCchemokine ligand CCL 5 and CXC-chemokine ligand 9/10, activated T cells move to and infiltrate tumor tissue in order to optimize the antitumor effect of their secreted effectors such as IFN-γ, tumor necrosis factor (TNF), perforins and granzymes [48]. MHC-I molecules primarily provide endogenous antigens to activate cytotoxic CD8+ T cells, while MHC-II molecules mostly present external antigens to activate CD4+ T helper cells [38]. The primary effector cells that cancer vaccines are predicted to produce are cytotoxic CD8+ T cells, which typically have a potent direct killing effect on target cells [22, 49].



 **Figure 4.** Mechanism of mRNA cancer vaccines [38].

## **Benefits of mRNA in autoimmune treatment**

 mRNA has therapeutic applications for the treatment of autoimmune and chronic cancers in addition to vaccines [50]. Corresponding to several clinical and medical research findings, mRNA can produce proteins that support the regulation of the immune system or promote tissue regeneration, which can lead to the treatment of cancer [51]. It might make it easier to create novel treatments for conditions including multiple sclerosis, rheumatoid arthritis and heart disease. A major advance in biopharmaceuticals is the development of vaccines based on mRNA. The manner that vaccines are developed and administered could be completely changed by this new platform. Furthermore, mRNA's potential as a therapeutic tool for

autoimmune and chronic diseases is an intriguing field of study with great implications for medical advancements. Most recent cancer technology is dedicated to advancing the study and development of mRNA and its applications as a top supplier of goods and services for the sector of life sciences. In order to facilitate the synthesis and distribution of mRNA-based medicines, this may involve developing new technologies or providing the materials and reagents required for mRNA synthesis in extremely large quantities for translation and delivery [52].

# **Treatment and prophylactic mRNA purification using affinity chromatography**

 Cancer treatment could be completely changed by the development of cancer vaccines, which offer a more individualized, targeted approach with fewer side effects than conventional cancer treatments [53]. The promise of cancer vaccines as an effective weapon in the fight against cancer is highlighted by their application in both cancer prevention and therapy. Immunizations against antigens associated with or specific to tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) have demonstrated potential to identify and eliminate cancer cells that overexpress particular antigens, resulting in a durable therapeutic response [54]. Cancer immunotherapy finds a unique and appealing target in TAAs and TSAs, particular chemicals expressed by cancer cells that are absent from normal cells. It is possible to teach the immune system to identify and eliminate cancer cells by immunizing people against antigens unique to the disease [55].

 To develop customized mRNA treatments, including patient-specific cancer vaccine or protein replacements for rare diseases, consistent, high-quality mRNAs are needed. IVT mRNA synthesis has many benefits, including simpler cell-free production, performance that is not dependent on the cell cycle, and an intracellular method for protein expression without the possibility of mutagenesis [56]. A new therapeutic and preventive technique that has the potential to revolutionize medicine is IVT transcribed mRNA. The encoding of antigen prote ns to trigger humoral and cellular immune responses is the purpose of IVT mRNA in the mRNA vaccines [57]. The structure of IVT mRNA is comparable to that of the endogenous mRNA found in eukaryotes. The representative structure of IVT mRNA is linear-type mRNA, but other mRNA forms have also been developed to achieve various goals by varying the patterns of protein production. The medication platform is characterized by incredibly quick development times and flexible production procedures. There are still issues with purification, even though mRNA quickly moved from clinical trials to commercialization. The impurities connected to the product and the process are produced by the cell-free production of mRNA, which increases the possibility of immunogenic reactions and reduces the product's translatability to the clinical settings [57]. The affinity chromatography is a useful primary capture step for separating functional transcripts from the product and some contaminants associated with the process. The disparities in capacity of non-amplifying, self-amplifying and trans-amplifying constructs with different strand lengths impede the development of platform procedures for the affinity purification of mRNA.

 Because of chemical modifications that enable stem cell engineering, protein replacement therapy, and cellular reprogramming, IVT mRNA is a potent alternative gene expression system with a wide range of applications in regenerative medicine, which is essentially necessary for therapeutic applications. The contaminants produced by in vitro transcription pose a serious threat to the secure delivery and long-term storage of mRNA, regardless of the product's size or intended use [58]. As existing commercially available products are mainly reliant on oligo-deoxythymidine ligand chemistries, affinity chromatography is a significant technique to overcome these obstacles. Although affinity chromatography is very useful for mRNA purification, it is unclear whether this technique will replace protein A in the production of mAbs, as it cannot separate important secondary structures such as double-stranded RNA.

 The mRNA vaccines against infectious diseases are the most recent application of IVT mRNA treatments [59]. Currently, a number of mRNA vaccines, starting with SARS-CoV-2, are being tested in clinical trials to combat infectious diseases such as HIV-I, Zika and rabies [60]. The outcomes of ongoing clinical trials with several mRNA vaccines have been summarized in [61]. In addition to the treatment of infectious diseases, immune-stimulating mRNA-based medicines have potential use in protein replacement therapies, immunotherapies and genome editing and reprogramming for cancer treatment. Lastly, as a novel medication candidate, IVT mRNA is likely to be employed in a number of therapeutic areas. mRNA vaccines will be particularly useful in pandemic scenarios since they allow for quick, scalable and affordable production. mRNA vaccines are expected to dominate vaccine types in the future, despite ongoing concerns regarding safety, the need for cold storage and the duration of antibody response [62].

# **Regulatory requirements for clinical trials of mRNA vaccines**

 Just as effective mRNA-based vaccines have prevented severe COVID-19, the technique is currently being researched for application against a variety of other infectious agents, including the herpes virus, respiratory syncytial virus (RSV), influenza and Zika virus [64]. Anti-cancer vaccines are also developed using the vaccine platform. Before beginning any human clinical trials, sponsors must file an investigational new drug (IND) application to the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) and obtain an IND number for biologics. When a drug is approved by the FDA, a federal agency under the Department of Health and Human Services, it signifies that the FDA has concluded that the drug is safe and effective for the purpose for which it is intended [65]. When the medication is used as prescribed by a licensed professional, its advantages outweigh its drawbacks. This is because the FDA regulates products that use mRNA as biologics. Sponsors may use the CBER's biologics license application (BLA) procedure to request permission to market an mRNA-based product, assuming the human trials are successful (see Table 1).



**Table 1.** Clinical trials of mRNA vaccines against infectious diseases [63].

 The COVID-19 pandemic caused a public health emergency, which is why Pfizer/BioNTech and Moderna were first granted emergency use authorizations (EUAs) for their mRNA-based COVID-19 vaccines [66]. However, subsequent BLAs, granted full clearance to both. A

commission known as the institutional review board (IRB), which oversees research ethics, must grant approval before beginning a clinical trial involving human participants. The group is known as an ethics committee (EC) in the EU and a research ethics board (REB) in Canada. The

ethical review commission (ERC) serves as an equivalent in Japanese culture.

### **Conclusion**

 Based on mRNA technology and other technological advances, what was once considered to be unattainable in cancer research is now possible. These advances have led to breakthroughs in the way that technology can detect, visualize and comprehend the treatment of cancer. The door to accelerating the fight against this illness may be opened by continuing to investigate and employ these technologies. The field of mRNA vaccine research has experienced a significant growth in recent years, with a particular focus on mRNA cancer vaccines. The selection and expression of antigens and targets, as well as the use of vectors and adjuvants, were all considered when analysing the most recent developments in mRNA cancer vaccines in this study. This allowed the study to reflect current trends and issues in cancer vaccine.

## **Authors' contribution**

 The conceptualization of the project was conceived by Emmanuel Adebola Adebanjo; Ugochukwu Okwudili Matthew supervised the research work; Kafayat Motomori Bakare was responsible for the validation and Victoria Enemona Oseni supervised the review and editing of the manuscript. All authors have read and approved the version of the manuscript for publication.

### **Conflict of interest**

 There is no conflict of interest in relation to this paper. However, U&J Digital Consult Limited, an IT and education consulting firm based in Nigeria, supported the research.

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