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Advances in mRNA Technology Beyond COVID-19 Vaccines

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Abstract:

The development and application of mRNA technology in humans over the past few years have resulted in great strides. Extensive work laid the scientific groundwork for these advancements. While the current pandemic has accelerated attention to mRNA-based therapies, we look beyond to other potential applications. We discuss current developments in mRNA technology beyond COVID-19 vaccines with a critical discussion of the challenges and potential of mRNA-based therapeutics in different diseases. We highlight the push towards personalized and more precise therapies in the medical field. The advent of modern gene-editing tools and deep sequencing provides a unique platform for the development of new therapies such as mRNA-based gene therapies. There is a significant focus on developing and screening delivery vehicles. The application of evidence-based targeted mRNA constructs can be used in gene editing via the generation, transcript repair, genetic replacement of transcripts, and at the protein level. We also briefly discuss the advantages and potential of these areas that currently we are not able to or have not convincingly matured into in mRNA technology as gene therapy. The remainder of the text discusses and condenses results showing what areas mRNA is being used in as potential gene therapies, as well as the strengths and weaknesses of the emerging approaches.

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INTRODUCTION

One of the most important biotechnological advancements of recent times has been the development of messenger RNA (mRNA) technology (May, 2021). This technology, though known for decades, began to rapidly advance, especially during the COVID-19 pandemic (Abbasi, 2020). Large investments were made to accelerate the vaccination development process, and a result was the successful deployment of COVID-19 mRNA vaccines (Jackson *et al.*, 2020). Last year alone, it was reported that billions of doses of the COVID-19 vaccines were rolled out globally (Kumar *et al.*, 2022). However, amidst such vaccine breakthroughs, the purpose of this essay is to track the advancements in the field of mRNA technology beyond vaccines (Knezevic *et al.*, 2021). Scientists have been working to develop innovative mRNA technologies, driving forward the potential of this highly flexible platform in different therapeutic and curative arenas (Jain *et al.*, 2021). The functioning of the genetic material, mRNA, is not limited to creating proteins in the body (Hogan and Pardi, 2022). Instead, it has applications in hair restoration, tissue repair, and cell regeneration, among many others (Brisse *et al.*, 2020). Research and experimentation take time, but the possibilities with this technology are infinite (Mueller, 2024).

At its core, the human body creates mRNA in a cell membrane and quickly translates its information into proteins (Mueller, 2024). In pharmaceutical and genetic studies, scientists can use this natural process to ask cells to produce any protein by providing the cell with a specific DNA sequence (Rohner *et al.*, 2022). In this way, mRNA technology can teach cells to create proteins that are part of a viral phase, causing the immune system to learn to recognize such proteins and initiate an immunogenic response (Chavda *et al.*, 2022). The range of possible therapeutic applications of mRNA goes far beyond traditional vaccines, including autologous or personalized cancer immune cell therapy (Damase *et al.*, 2021). They showed enthusiasm for the potential of mRNA to target the cells of the human body to boost the immune system's ability to attack cancer cells and pave the way for this affirmation (Al Fayez *et al.*, 2023). The technology is already elevating the field of oncology and hematology and can also be exploited for autoimmune or metabolic diseases (Weng *et al.*, 2020). For example, in a clinical trial that began in 2017, researchers achieved favorable tumor responses in patients with melanoma, adenocarcinoma, and squamous cell carcinoma, among others (Anand and Stahel, 2021).

The Science behind mRNA Technology

The existing knowledge of mRNA and other relevant biomolecules provides the necessary foundation for readers to approach the wider discussion of mRNA-based treatment approaches. Initially, mRNA, or ribonucleic acid, exists inside the cell as a chain of nucleotides that consists of a sugar, a phosphorus group, and one of four bases (Jain *et al.*, 2021). Transcription, converting the genetic code of a gene into a complementary stretch of mRNA, and translation, the process of turning mRNA code into an amino acid sequence, are the two primary processes concerning mRNA (Weng *et al.*, 2020). Translation occurs on a structure inside the cell called the ribosome, where transfer RNA reads complementary mRNAs with the appropriate triplet amino acid code and creates peptide bonds to form a polypeptide chain, resulting in the final protein (Liu *et al.*, 2023). There is also another form of RNA, called transfer RNA, which serves as the link between the mRNA and the protein, bringing the matching amino acid to the site of protein synthesis (Antonarelli *et al.*, 2021). These translation events form the basic concept of using synthetic mRNA for therapeutic purposes. Simply put, synthetic mRNA is created and inserted into the cytoplasm of the cell, where translation and polypeptide synthesis begin (Anand and Stahel, 2021). This is achieved through a series of mechanisms. mRNA needs a way to enter the cell and also avoid being dismantled by cell mechanisms, specifically the endosomal pathway and the ribonuclease, in order to function properly (Al Fayez *et al.*, 2023). In recent years, technological advancements have resulted in a number of processes and pathways that increase the efficacy and safety of

mRNA vaccines and therapeutics (Rohner *et al.*, 2022). Specifically, the use of lipid nanoparticles for the delivery of mRNA into cells has been a major breakthrough (Chavda *et al.*, 2022). The development of mRNA as a therapy is accompanied by extensive preclinical and clinical research highlighting both the efficacy and safety of use (Liu *et al.*, 2023). One major challenge to mRNA-based therapies is their low stability, which requires the use of cold storage techniques to maintain their structural integrity and function (Antonarelli *et al.*, 2021).

Applications of mRNA Technology in Medicine

The advent of immune checkpoint blockades in the past decade has demonstrated the impressive anti-cancer potential of T cell activation (Jahanafrooz *et al.*, 2020). The data obtained from these therapies have also revealed that different antigens—neoantigens derived from non-synonymous mutations with high single-nucleotide variations in coding regions and differentiation antigens such as melanoma-associated antigens—can activate the immune system to similar extents in different individuals (Miao *et al.*, 2021). The results highlight the importance of the immune system in achieving anti-tumor responses and have led to innovative strategies to activate the immune system using whole tumors, tumor lysates, or DNA coding for tumor antigens, termed cancer vaccines (Huang *et al.*, 2021). Essentially, vaccines introduce tumor-associated antigens into the body as antigens to stimulate adaptive immunity and activate T lymphocytes (Beck *et al.*, 2021). mRNAs can encode the same antigens as those of DNA and have the additional advantages of rapid and efficient large-scale production and proper in vivo translation, strengthening the effect of immuno-activation (Saxena *et al.*, 2021).

mRNA vaccines are ideal for protecting against rapidly evolving pathogens (Abbasi, 2020). They are produced using the sequence of a virus or bacterial surface antigen, which is then provided to B cells in the host for the production of pathogen-specific neutralizing antibodies (Jackson *et al.*, 2020). Thus, mRNAs can be utilized to develop vaccines against various diseases (Iqbal *et al.*, 2021; Kumar *et al.*, 2022). For example, research into mRNA vaccines for Zika fever and rabies is already underway (Knezevic *et al.*, 2021). The success of mRNA vaccines has considerable implications for the rapid generation of vaccines in the future and could revolutionize future vaccine development (Jain *et al.*, 2021).

Current gene therapy technologies target the gene of interest; those that insert a missing gene depend on the tissue type as do other insertional gene therapy approaches (May, 2021). This represents a significant advance, but smaller indirect gene therapy approaches could enable wider targeting and be amenable to different tissues and organs (Abbasi, 2020). mRNAs can encode various types of genes of interest (Jackson *et al.*, 2020). As such, they can be used to express photoenzymes, transcription factors, or proteins with enzymatic roles to compensate for genetic anomalies at cellular levels (Kumar *et al.*, 2022). For example, in a rare genetic disorder in which a gene encoding for an ion channel is dysfunctional, ion channel-encoding mRNA can be injected into patients' tissues to provide an alternative therapeutic effect (Knezevic *et al.*, 2021). So far, most trials are focused on genes of interest to create functional proteins and enzymes (Jain *et al.*, 2021). These can restore physiological activity via an entirely different pharmacological or cellular-based approach (Brisse *et al.*, 2020; Hogan and Pardi, 2022; Mueller, 2024).

Cancer Immunotherapy

The COVID-19 pandemic has brought messenger RNA (mRNA) technology into the spotlight due to allowing the rapid generation of effective and safe vaccines. While unprecedented, recent events overshadow the fact that significant advances in mRNA technology have been made over a few decades, resulting in clinical-grade mRNA products (Iqbal, 2021; Rohner *et al.*, 2022). Research towards utilizing these advances to develop novel immunotherapies, including for cancer, has gained much attention and critical evaluation due to intrinsic limitations of the vaccine field (Al Fayez *et al.*, 2023). However, an attempt to provide an exhaustive overview of

the entirety of mRNA-based cancer immunotherapies is out of this article's scope (Weng *et al.*, 2020). Schematically, mRNA vaccines can be made to encode either tumor-associated antigens or neoantigens, the non-tumor-specific and tumor-specific proteins, respectively portrayed above (Anand and Stahel, 2021). To elicit strong and sustainable immune responses against cancerous cells, mRNA vaccines may thus trigger immune systems via different arms of the immune system (Brisse *et al.*, 2020).

Some notable success stories from clinical trials of mRNA vaccines are achieving complete remission in patients with high-risk melanoma or mild hematological malignancy, improved overall survival in various cancers, prolonged disease control, and improved progression-free survival after failure of therapy in solid tumors (Abbasi, 2020). An important next step is the development of truly personalized cancer vaccines, which we discuss in the last subsection (Kumar *et al.*, 2022). Importantly, combining vaccines with other treatment modalities often goes beyond changing the response modifiers in the clinical trial (Knezevic *et al.*, 2021). In this article, we discussed only those studies that use mRNA vaccines to demonstrate structural updates within the tumor immunological microenvironment when given alone (Jain *et al.*, 2021). Key data from studies indicating immunological changes outside of cancer/tumor-immunity sites are included (Hogan and Pardi, 2022). However, of note, several of the studies referred to here contain subgroup analyses in combination with other treatments that can provide additional insight into the agent's clear activity as a vaccine treatment when given as monotherapy (Brisse *et al.*, 2020).

Infectious Diseases

Influenza Virus Beyond COVID-19, it has been envisioned that mRNA technology could be used for future vaccine development of human pathogens, such as influenza and Zika viruses (May, 2021). Influenza viruses cause seasonal flu and, more importantly, infections with novel seasonal or pandemic strains are potentially very severe due to a lack of or low societal immunity (Abbasi, 2020). Influenza vaccines typically have lower efficacy or no marked effect at all in the elderly or in young children, which is a direct consequence of the lower responsiveness of their immune systems (Jackson *et al.*, 2020; Wu *et al.*, 2024). In addition to complicated and time-consuming production, current seasonal vaccines have to be produced annually, and their formulations have to be adapted to circulating viral strains predicted several months in advance (Kumar *et al.*, 2022). This year-long process carries the added risk that when a vaccine is finally distributed, the virus has mutated further (Knezevic *et al.*, 2021). Furthermore, phylogenetically constantly changing and mutated strains pose the possibility of a devastating pandemic, which has happened several times over the last century (Jain *et al.*, 2021). Nanotechnology, as well as the mRNA platform, can be used for creating universal vaccines that are designed to raise antibodies cross-reactive to an extensive number of influenza strains (Hogan and Pardi, 2022). Such vaccines are anticipated for T cell activity that would protect broadly against multiple influenza A strains. An effort is currently focusing only on leading group 1 influenza A strains (Brisse *et al.*, 2020). Vaccines will provide wide-ranging preventative protection to the populations, and such a vaccine will be sought by the next flu pandemic (Mueller, 2024). There is a massive scope for further exploration of the mRNA platform for the same benefits in developing countries. mRNA vaccine-induced robust immune responses have proven to be safe and effective in the fight against infectious diseases (Rohner *et al.*, 2022). Emerging and re-emerging infectious diseases that are major public health problems, particularly in developing countries, cause far more than ecological and socio-political instability (Chavda *et al.*, 2022; Iqbal, 2022). However, on the other hand, vaccine hesitancy, lack of understanding, affordability, acceptability, and infrastructural challenges for mRNA vaccine production and distribution are the main obstacles to access to mRNA vaccines, undermining the exploitation of mRNA vaccine potential (Al Fayez *et al.*, 2023). It is a new format for category consistency testing (Weng *et al.*, 2020). This is a universal vaccine platform

(Ahed, 2021; Alkhatib, 2020). During the pandemic phase, it is time to prepare for the quick distribution and quick reaction phase (Alkhatib and Alqarar'a, 2023). Vaccine accessibility is a major factor in deciding the growth of meticulous use and efficacy. Difficulties in regulatory policies and the development of the industry may prove to be catastrophic (Alazzam *et al.*, 2022). Even though the current scenario gives an advantageous opportunity, the aforementioned concern is quite clear (Brisse *et al.*, 2020). However, mRNA vaccine can be an alternative to existing conventional vaccines for global health security and pandemic containment (Mueller, 2024).

CONFLICT OF INTEREST

Authors hereby declare that they have no conflict of interest.

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