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"REDEFINING IMMUNIZATION: MR NA-BASED THERAPEUTICS BEYOND VACCINES – CURRENT ADVANCES AND FUTURE DIRECTIONS"

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ABSTRACT

To conduct a non-randomised, prospective study of mRNA technology, a cutting-edge technology that uses synthetic mRNA to guide cells to produce specific antigens, proteins or to trigger an immune system that can be used to treat diseases. It also channels the natural process where cells translate genetic information from their genetic material to produce proteins. The main components of this technology include mRNA, LNPs and a mature protein expression, which is highly acclaimed in its use in the production of vaccines. While mRNA technology gained global attention during COVID- 19 era but its potential extends beyond just vaccines; it is also used in cancer immunotherapy, where the mRNA sequences encode tumour-specific neoantigens to increase the immune system against cancer cells, Protein Replacement theory is also a great brainchild of mRNA technology where it can encode functional proteins to compensate for missing or defective ones caused due to genetic mutations. Despite its promise, mRNA technology faces several scientific, technical and regulatory hurdles. The main challenge which are faced is Stability and storage, where mRNA is inherently unstable and can degrade rapidly, the need is to develop thermostable mRNA formulations. The context and promise of this aspiring technology is explained in this review as further.

KEYWORDS: mRNA therapeutics, gene therapy, personalized medicine, cancer immunotherapy, rare diseases.

INTRODUCTION

Vaccines play an important role in society to build immunity in humans from birth. So, the role of vaccines is very crucial compared to that of other pharmaceutical goods. Since vaccines are solely responsible for building a foundation for growth, it is the only major pharmaceutical preparation which is being independently injected into a newborn's anatomy to seed a strong basis for its immunity.[1] Vaccines are biological preparations which assist in providing immunity to specific infectious. There are specific vaccines which provide immunity towards specific infections which are available in the market. They work by stimulating the body's immune system to identify and fight against pathogens like bacteria or viruses. The mRNA technology is a groundbreaking biomedical invention which utilises the messenger RNA(mRNA) to develop a specific protein by instructing the cells, which trigger the immune system to give a therapeutic effect. mRNA is the genetic material that carries information from the DNA, converting it to ribosomes by the cell's protein-making machinery.[2] After the COVID-19 vaccine manufactured by Pfizer, this technology has gained widespread attention due to its speed and potential to revolutionise modern medicine. The mRNA serves as a cosmopolitan platform, which, when the lipid nanoparticles are delivered, the mRNA sequence can be altered quickly to change any protein or disease, from cancer antigens to genetic disorders.[3]

Mechanism of Action of mRNA Therapeutics

The importance of the effectiveness of the mRNA therapeutics is solely dependent on their delivery. Since mRNA is large in size, negatively charged and prone to degradation, it needs a higher degree of protection in its delivery to ensure that it reaches the target cells intact and functional. The key delivery system for mRNA therapeutics includes

- Lipid Nanoparticles (LNP)

It is the clinically approved mRNA delivery system, which is also widely used.

Its components include

Ionizable lipids: They can bind with mRNA electrostatically

Cholesterol : Acts as a lipophilic and assists in membrane fluidity

PEG- lipids : It provides stability and improves circulation time

Phospholipids : Act as the basis for forming the bilayer structure

The mechanism of LNPs acts by the process of endocytosis, where the LNPs encapsulate the mRNA. When the lipids enter the acidic endosomes, these ionizable lipids become charged, turning off the membrane, which releases the mRNA into the cytoplasm.[4] These Lipid Nanoparticles with mRNA revolutionised the world with COVID-19 vaccines, which were manufactured by Moderna and Pfizer-BioNTech Mostly assisted with mRNA cancer vaccines

For Protein replacement therapies

- Polymeric Nanoparticles

Polymeric Nanoparticles are made up of biodegradable polymers like PEI (Polyethyleneimine), PLGA Poly(lactic-co-glycolic acid). It is environment-friendly, biodegradable and is useful for release kinetics. The only drawback is that it can be cytotoxic at higher doses.[5]

- Lipid-Polymer Hybrid Nanoparticles (LPHN)

Lipid-Polymer Hybrid Nanoparticles are a hybrid system which combines the stability of polymers with the biocompatibility of lipids. The structure of lipid-polymer hybrid nanoparticles is composed of a polymeric core with a lipid shell which encapsulates the mRNA. The major use of LPHN is in the treatment of cancer immunotherapy and for the Central Nervous System targeted drug delivery.

- Exosomes

These natural vesicles secreted by animal cells are innovated to hold therapeutic mRNA. It is considerably low toxic compared to other carriers and has specific tropism towards specific body cells, which are complex to produce on a larger scale.[6]

- Cationic Peptides

Cationic peptides or proteins are positively charged protein structures which form complexes with negatively charged mRNA. These positively charged peptides are used for local mRNA delivery for localised infection and wound healing. It is also used in targeted gene expression in carcinogenic cells.[7]

Comparison with DNA-based therapies

DNA-based therapy, also called gene therapy, is a novel approach which uses genetic material to treat or prevent disease by altering an individual's genetic makeup. It introduces new genetic material into cells to correct faulty genes and has the ability to alter how genes are expressed.[8] The comparison of DNA-based therapy with RNA therapeutics can be seen in the following table.

Table 1: Comparison of DNA and mRNA-based therapies.[9,10,11,12]

S.No	Category	mRNA-Based Therapy	DNA-Based Therapy
1	Mechanism of Action	Direct translation in the cytoplasm	Requires nuclear entry and transcription
2	Location of Action	Cytoplasm	Nucleus
3	Time to Effect	Rapid (immediate protein production)	Slower onset (due to nuclear entry and transcription)
4	Integration into Genome	No (non-integrative)	Possible (especially with viral vectors)
5	Process	mRNA → Protein	DNA → mRNA → Protein
6	Duration of Expression	Short-term (hours to days)	Long-term (days to years, or permanent)
7	Mutagenesis Risk	Minimal	Potential (insertional mutagenesis if integrated)
8	Immune Response	Lower (especially with modified nucleosides)	Higher (especially with viral vectors)
9	Targeting Requirements	Only needs to reach the cytoplasm	Must cross the nuclear membrane
10	Stability	Less stable; cold chain required	More stable, less cold-chain dependent
11	Immune Response	Lower (especially with modified nucleosides)	Higher (especially with viral vectors)
12	Production	Synthetic, scalable, fast	More complex (especially viral vector production)
13	Storage	Cold storage (e.g., -20°C or -70°C for some vaccines)	Stable at higher temperatures
14	Safety Profile	High (no integration, transient expression)	Lower (risk of integration and prolonged expression)
15	Regulatory Approvals	Multiple (e.g., COVID-19 vaccines)	Fewer, under development for gene therapy
16	Applications	Vaccines, cancer immunotherapy, protein replacement, CRISPR	Gene therapy, inherited disorders, DNA vaccines, long-term editing
17	Suitable for	Rapid response (e.g., pandemic vaccines), temporary therapies	Long-lasting effects, gene correction, and hereditary disease treatment

Therapeutic Applications Beyond Vaccines

- mRNA-based personalised cancer vaccines

It was discovered in the 1990s that mRNA could directly transfect muscle cells when administered in vivo, resulting in the production of the corresponding protein that was encoded. This discovery marked the beginning of the mRNA vaccine. However, the absence of effective synthesis, modification, and delivery technologies limits its clinical applicability. With the success of COVID-19 vaccines and other recent advancements, there is now hope that mRNA-

based treatments will be used to treat a variety of illnesses, most notably cancer. Therapeutic mRNA cancer vaccines have attracted a lot of attention as a unique immunotherapeutic approach that uses antitumor adaptive immune responses to kill tumour cells by tumour-specific antigens (TSAs), tumour-associated antigens (TAAs), and immune modulatory proteins.[13] Compared to conventional inactivated pathogens or protein-based vaccinations, therapeutic mRNA cancer vaccines have been shown to offer greater cellular or humoral immunity. Since mRNA cancer vaccines can elicit a systemic immune response, it has been demonstrated to be helpful for metastatic tumours that are difficult to cure surgically. Aside from this, mRNA cancer vaccines have the ability to create and preserve long-term immunological memory, which enables the prevention of tumour recurrence. Because of their great versatility, mRNA vaccines make it simple to modify mRNA sequences to encode specific antigens or cytokines that are useful in the fight against cancer, which can help with personalised treatments, which can improve treatment outcomes and reduce adverse effects. As of right now, the most beneficial use of mRNA vaccines in oncology is the delivery of mRNAs that express TAAs. TAAs are self-antigens that are deliberately produced in tumour cells, while they can also exist at some concentrations in healthy cells. Overexpressed self-antigens, cancer-testis antigens (CTAs), and oncofetal antigens are common candidates for TAAs. In 1995, the carcinoembryonic antigen (CEA) was used as the target for the first effort at TAA mRNA vaccines in cancer therapy. TAAs are characterised by low immunogenicity and tumour specificity, as well as high immunological tolerance and low vaccination potency, because of the autogenous property.[14] To get around these drawbacks, using mRNA encoding numerous TAA mixes is becoming more and more common as a way to improve the effectiveness of cancer vaccines for different kinds of cancer. TSA also called as Neoantigens, which are absent from normal cells, are produced by somatic mutations that occur randomly in tumor cells. Neoantigens are a desirable target for cancer vaccines because the host immune system may recognise them as a "non-self" theme.

TSA-specific vaccines may cause both peripheral and central tolerance reactions, which would reduce immunisation effectiveness. Nowadays, the main targets of mRNA vaccines are tumour-specific antigens, also known as neoantigens.[15]

- Ongoing trials

Currently, there are fifteen clinical trials carried out on TAA-encoded mRNA vaccines. Transmembrane phosphatase with tensin homology (TPTE), tyrosinase, melanoma-associated antigen A3 (MAGE-A3), and New York oesophagal squamous cell carcinoma 1 (NY-ESO-1) are

among the four melanoma-associated antigens (MAAs) encoded by the BioNTech BNT111 mRNA cancer vaccine, which is in phase two clinical trial. Moderna's mRNA-2416, which is in a phase 1 trial, encodes OX40L, was safe and tolerable when injected intratumorally. It also displayed widespread proinflammatory activity and desired TME alterations. These results offer strong evidence in favour of its further study in combination therapy with durvalumab, an anti-PD-L1 inhibitor, for solid malignancies. Similarly, in a dose escalation study (NCT03739931), co-administration of durvalumab and mRNA-2752 encoding OX40L/IL23/IL36g demonstrated anticancer benefits, confirming the promise of mRNA cancer vaccines as a treatment strategy.[16]

B. Genetic and Rare Diseases

- Protein replacement via mRNA (e.g., cystic fibrosis, muscular dystrophy)

A rare genetic disease is a condition that affects only a small portion of people, which is brought on by a mutation in a person's DNA. If an illness affects less than 1 in 2,000 persons, it is deemed rare in the majority of countries. Although some of these illnesses can develop on their own as a result of novel mutations, most are inherited. These mutation in genes causes a lack of enzymes or proteins, which leads to disease conditions (eg, cystic fibrosis, muscular dystrophy).[18] The therapeutic protein encoded in mRNA is complexed into an appropriate non-viral nucleic acid delivery formulation and administered intravenously to the patient. By entering the cell through endocytosis, the mRNA formulation can express the therapeutic protein in the patient's blood, muscle, or liver cells, among other cell types, and mediate symptomatic treatment. This is called as mRNA replacement therapy. Bypassing the procedures necessary for protein expression and purification in existing recombinant protein-based biotherapeutics, such as ERT (enzyme replacement therapy), this mRNA therapy significantly lowers treatment costs.[17]

mRNA replacement therapy for cystic fibrosis

cystic fibrosis is a rare condition brought on by a malfunction in the cystic fibrosis transmembrane conductance regulator (CFTR). Chloride/bicarbonate ion transporter CFTR is expressed by secretory epithelial cells in the gastrointestinal tract, lungs, and respiratory epithelium. Along the concentration gradient on the surface of epithelial cells, CFTR helps transport chloride/bicarbonate ions, and because of osmosis, it permits hydration at the cell surface. An ionic imbalance within cells and the development of dried mucus at the cell surface are caused by a protein deficiency. In the study by Haque et al., CFTR mRNA-nanoparticles were created by complexing the nucleoside-modified mRNA with positively charged chitosan

and poly-D, L-lactide-co-glycolic acid (PLGA).[18] Remarkably, the study found that the CFTR mRNA containing 50% nucleoside-modified pyrimidines (Thiol-UTP and 5-methyl cytidine) had no immunological costs and was better at expressing CFTR in the lungs than the mRNA containing 100% modified pyrimidines (1-methyl pseudouridine and 5-methyl cytidine). Phase I trials for Vertex Therapies' CFTR mRNA therapy candidate VX-522 were initiated in 2022 in collaboration with Moderna (NCT05668741, 2022). Using their LUNAR-LNP platform, Arcturus Pharmaceuticals also launched CFTR mRNA treatment at the same time (NCT057125382023).

C. Regenerative Medicine

mRNA encoding for growth factors

Growth factors are bioactive polypeptides with biological activity that control vital cellular functions like migration, differentiation, proliferation, and survival. Though their clinical utility has been limited by issues including short half-lives, high production costs, and poor tissue penetration, growth factors have historically been administered as recombinant proteins in therapeutic situations. In molecular medicine, messenger RNA (mRNA)-based treatments are a revolutionary development.[17] Growth factors and other therapeutic proteins can now be encoded by mRNA thanks to recent advances in mRNA stability, delivery methods, and translational efficiency. In fields such as tissue engineering, wound healing, heart repair, and bone regeneration, this method presents a viable substitute for recombinant protein delivery.

Potential in tissue engineering

Cardiovascular regeneration: VEGF-A mRNA (AZD8601-Moderna/AstraZeneca) is delivered into the infarct or peri-infarct zone as localised nanoparticle injection or biodegradable hydrogel to induce local blood vessel formation in myocardial infarction (MI). VEGF-A is the target growth factor that initiates angiogenesis, endothelial cell proliferation. It is in a phase 1 clinical trial (EPICCURE) in patients undergoing coronary artery bypass grafting (CABG).

Bone and Cartilage regeneration: BMP-2 mRNA is delivered into bone by using collagen sponges, PLGA scaffolds, or hydrogels to restore bone formation in osteoarthritis and fractures. BMP-2 is the target growth factor which restores bone formation in rats. TGF-β1 mRNA showed hyaline cartilage repair in osteochondral.

Kidney and Liver repair: HGF mRNA is administered as LNP-encapsulated mRNA intravenous injection to treat Acute kidney injury (AKI) and hepatic damage (e.g., ischemia-reperfusion

injury, fibrosis), which lacks efficient treatments.[18] It showed reversal of fibrosis, reduction of inflammation, and enhanced functional recovery in rodents. HGF is the target growth factor that acts as anti-fibrotic, anti-apoptotic, and promotes regeneration. EGF mRNA shows tubular structure regeneration and restores serum creatinine to baseline levels post-injury.

Skin and Wound healing: Biocompatible mRNA hydrogel dressings encoding target growth factor PDGF-BB and FGF-2 showed accelerated wound closure, increased granulation of tissues and organised collagen deposition.

Neural regeneration: Nerve growth factor (NGF) is a common treatment approach for treating peripheral nerve abnormalities in Alzheimer's disease because it encourages the survival, proliferation, and neurite outgrowth of neuronal cells. However, individuals may experience excruciating agony when NGF is administered clinically. Thus, NGFR100W mRNA, a chemically altered NGF mutant, offers an alternative to direct NGF treatment by dramatically lowering nociceptive activity by LNP administration. Miyuki Baba et al. studied the intranasal injection of complexed nanomicelles to deliver brain-derived neurotrophic factor mRNA in a mouse model.[19] This improved neuronal recovery of olfactory function and returned the olfactory epithelium to a structure resembling normal.

D. Autoimmune and Inflammatory Disorders

- Modulating immune response through transient mRNA expression

In transient mRNA expression, therapeutic proteins or antigens (such as cytokines, immunological checkpoint inhibitors, and regulatory transcription factors) can be temporarily produced without affecting the genome, providing a potent way to control the immune response by introducing synthetic messenger RNA into cells. Depending on the goal and situation, this method uses the body's built-in protein synthesis machinery to either trigger tolerance or immunological activation. It's commonly employed in cancer immunotherapy, vaccine research, and the treatment of inflammatory or autoimmune illnesses. The potential of long-term adverse consequences is decreased by the temporary nature of mRNA, which guarantees regulated, brief protein expression. Furthermore, mRNA therapies are non-integrative and quickly configurable, which makes them a secure and adaptable platform for immune regulation. In addition to its role in the pathophysiology of inflammatory and autoimmune diseases, mRNA also has potential therapeutic applications.[20] The overproduction of pro-inflammatory cytokines like TNF-α, IL-6, and type I interferons is caused by deregulation of mRNA expression in a number of autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, and systemic lupus

erythematosus. Furthermore, anomalies in the splicing or alteration of mRNA can produce new autoantigens that set off immunological responses against the body's own tissues. Through receptors like TLR7 and TLR8, the innate immune system may also mistakenly perceive endogenous or altered mRNA as alien, which can lead to persistent inflammation. mRNA is being investigated as a potential new medicinal approach. There is potential for treating conditions like multiple sclerosis and type 1 diabetes with tolerogenic mRNA vaccines, which are being developed with the goal of teaching the immune system to tolerate particular self-antigens.

Additionally, mRNA can be utilised to deliver gene-editing tools like CRISPR-Cas9 to repair immune dysregulation at the genetic level or to express anti-inflammatory proteins like TGF-β or IL-10. To prevent unintended immune activation, these strategies make use of sophisticated delivery mechanisms, such as lipid nanoparticles, and carefully alter mRNA.

All things considered, mRNA has enormous promise for both comprehending illness mechanisms and creating focused treatments for inflammatory and autoimmune disorders.[21]

Advantages of mRNA Therapeutics

The advantages of mRNA in the domain of healthcare have no bounds where it can provide numerous benefits in treating diseases which were ought to known non-curable. The advantages of mRNA Therapeutics are as follows

- It is non-infectious and can not replicate, which reduces the risk of unknown effects
- The production of scalable products is possible using synthetic, cell-free methods
- It is highly personalised medicine where it can be made specific to the individual specific treatments.
- It is highly acclaimed for the production of vaccines due to its highly immune-stimulating response.
- It provides transient protein expression, which is ideal for localised therapeutic effects
- Due to its null risk of genomic integration, it can minimise the safety concerns like insertional mutagenesis.
- It is applicable for diverse diseases, including cancer, infectious diseases and rare disorders
- Used for targeted drug delivery via lipid nanoparticles and other carriers
- It can be easily altered for the specified use, which can also be applied to treat diseases caused by viruses

- Non-contaminative effect due to cell-free and sterile production, which reduces the infection risk.[22]

The list of advantages can be measured by the following table

Table 2: Advantages of mRNA Therapy.[23]

S.no	Advantages	Explanation
1	Safe and Non-Infectious	mRNA is non-infectious as it doesn't use any viral vectors, reducing the risk of complications
2	Transient Expression	Since mRNA degrades over time, it can be easily used to treat localised infections
3	Rapid and Scalable Production	mRNA can be synthesised swiftly using in vitro transcription, which can be easily scaled large during emergent pandemics
4	Synthetic	Non-involvement of cellular or biological materials, which reduces the contamination risks
5	Targeted Delivery	Encapsulated in nanoparticles for targeted delivery
6	Customizable	Can be easily encoded to produce enzymes, antibodies or cancer antigens
7	Impressive Immune Response	Useful in vaccines, mRNA, which can stimulate cellular and humoral immunity
8	No Risk of Genomic Integration	Unlike gene therapy, it doesn't cause any genomic damage.
9	Easily Modifiable	Especially in vaccines, mRNA for new virus strains
10	Applicable across Diseases	Can be used to treat cancer, rare genetic diseases and protein replacement therapies.

Challenges and Limitations

- Stability and storage issues

As mRNA is delicate and susceptible to enzymatic, thermal, and moisture destruction, storing and managing mRNA vaccines can be extremely difficult. These vaccines frequently need to be stored at extremely low temperatures (such as -70°C for Pfizer-BioNTech's vaccine), which makes distribution more difficult, particularly in places with limited resources. Lipid nanoparticles (LNPs), which shield mRNA but are also susceptible to environmental changes, are chemically altered to increase stability. To extend shelf life, techniques like lyophilisation (freeze-drying), buffer modification, and cryoprotectants are employed. To lessen reliance on the cold chain and increase the accessibility and viability of mRNA vaccines for use worldwide, research is being done to create thermostable formulations and alternate delivery methods.[24]

- Delivery system hurdles

mRNA vaccine delivery faces several key challenges due to the fragile and unstable nature of mRNA, which is easily degraded by enzymes in the body. To protect it, mRNA is encapsulated in lipid nanoparticles (LNPs) that aid in cellular entry and endosomal escape. However, LNPs can trigger immune responses or cause inflammation. Additionally, unmodified mRNA can activate innate immunity, reducing vaccine efficacy, which is mitigated using modified nucleosides. Efficient and targeted delivery to specific tissues without off-target effects remains difficult, and large-scale production demands complex, precise manufacturing and quality control processes.[25]

- Immunogenicity and safety concerns

Despite its great effectiveness, mRNA vaccination treatment has certain safety and immunogenicity issues. By stimulating pattern recognition receptors such as TLRs, the synthesised mRNA can elicit significant innate immune responses, which may result in inflammation and a decrease in antigen expression. To increase stability and lessen undesired immunological activation, modified nucleosides such as pseudouridine are employed. Infrequent allergic reactions, myocarditis, and possible autoimmune reactions are among the safety concerns, albeit they are still infrequent. Delivery-related lipid nanoparticles may potentially result in systemic or local adverse consequences. The goals of ongoing research and surveillance are to guarantee a positive risk-benefit profile in therapy, enhance formulation, and lower adverse events.[26]

Recent Clinical Trials and Approvals

The current clinical pipeline for mRNA therapeutics proves to be of broad versatility, with the scope of technology beyond COVID-19. Highly acclaimed pharmaceutical companies like Moderna, BioNTech and others have advanced with numerous mRNA therapeutics for a wide range of diseases, including cardiovascular conditions, genetic disorders, cancer and infectious diseases.

The list of companies which is ongoing with clinical trials for mRNA therapeutics.

Table 3: Ongoing Clinical Pipeline for mRNA Therapeutics.[27,28]

S.no	Therapeutic	Developer	Indication	Clinical phase	Key Notes
1	mRNA-3927	Moderna	Propionic acidemia	Phase 2	For a rare metabolic disorder
2	mRNA-	Moderna &	Melanoma	Phase 3	Personalized neoantigen

	4157/V940	Merck	(cancer vaccine)		vaccine
3	mRNA-4359	Moderna	Solid tumours (checkpoint cancer vaccine)	Phase 2	Immunotherapy for multiple tumour types
4	mRNA-0184	Moderna	Heart failure (relaxin hormone)	Phase 1	Promotes vasodilation
5	mRNA-3705	Moderna	Methylmalonic acidemia	Phase 2	Liver-targeted delivery for Genetic disorders
6	mRNA-1403/1405	Moderna	Norovirus vaccines	Phase 2/3	For global protection
7	mRNA-1647	Moderna	Cytomegalovirus (CMV) vaccine	Phase 3	Multi-antigen vaccine for reproductively active women
8	mRNA-1010/1020/1030	Moderna	Seasonal influenza	Phase 2/3	For the Multivalent flu vaccine
9	mRNA-1345 (mRESVIA)	Moderna	Respiratory syncytial virus (RSV)	Phase 4 (Commercial)	Approved for use in geriatrics, the first mRNA RSV vaccine
10	UX053 (LUNARGSD3)	Ultragenyx	Glycogen storage disorder type III	Phase 1	For a rare genetic condition
11	BNT-141	BioNTech	Solid tumours (various)	Phase 1	Lipid nanoparticle delivery for multi-tumour targets
12	Autogene Cevumeran	BioNTech & Genentech	Pancreatic and colorectal cancers	Phase 2	For personalised cancer vaccine using 20 anti-neoantigens
13	OTX-2002	Omega Therapeutics	Hepatocellular carcinoma	Phase 1	First-in-class mRNA epigenetic controller.

Future Prospects

The future of mRNA therapeutics is extremely promising, with the power to transform multiple domains of medicine. The overwhelming success of mRNA vaccines during the COVID-19 pandemic has accelerated the health of the entire world, acting as the perfect shield in emergent pandemic situations. The mRNA therapeutics are expected to expand significantly into personalised medicines, mainly in the scarce successful stream like oncology. It is used to train the immune system using specific tumour antigens, which have shown promising results as a standard in cancer immunotherapy. More than cancer, it is a great tool in treating hereditary diseases, which can deliver functional proteins which can compensate for genetic malfunctions, which can offer a new hope to untreatable disorders. In cases of infectious diseases like Respiratory syncytial virus, HIV and influenza, mRNA vaccines are in clinical trial phases to prove their safety and efficacy.[29]

Artificial Intelligence (AI) is a revolutionary tool to change the aspects of all domains in the future. It is mainly used in the development of mRNA therapeutics, which is used in optimising mRNA sequences for translation, efficacy, greater stability and reduced immunogenicity. The important goal of mRNA sequence optimisation is to provide synthetic mRNA to produce high and sustained levels of target protein in human cells without causing any immune defence or degradation. AI also helps in identifying the optimal 5' and 3' UTR sequences. Tools with AI algorithms are under development to reduce immunogenic motifs, to predict mRNA folding patterns which can resilient enzymatic degradation.

The next generation of delivery technologies is under development to produce a higher rate of efficacy. The de-novo delivery technologies for mRNA therapeutics include.

Hydrogel and Microneedle Technology: This technology offer local, sustained release of delivery of mRNA, which can be highly useful in the treatment of regenerative vaccines, dermatological applications and cancer vaccines.

Self-Amplifying mRNA(saRNA) : Even though it is not a delivery system, saRNA lowers the amount of mRNA which is needed to allow replicate within cells, lowering the burden on delivery vectors and expanding formulation flexibility.[30]

CONCLUSION

mRNA technology represents a huge gradient transformative advancement in modern medicine, which offers a flexible and rapid platform in the development of the future of therapeutics. It has gained global recognition due to its implemented achievement in COVID-19 vaccine development, its true potential is unveiled in the treatment of genetic disorders, cancer and also plays a key role in regenerative medicine. Despite its challenges, such as delivery limitations, manufacturing complexity, and ongoing research, delivery limitation and innovation continues to define and refine its uses to expand. With this development of omnipotent delivery systems, personalised therapies and scalable production methods, the future of healthcare is better poised to play a role in precision medicine and next-generation therapeutics.

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