

Review

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Posted Date: 9 May 2025

doi: 10.20944/preprints202505.0377.v1

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Review

mRNA Vaccine Technology Beyond COVID-19

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Abstract: Background/Objectives: Since their approval in early 2020, mRNA vaccine has gained significant attention since COVID-19 pandemic as a potential therapeutic approach to tackle several infectious diseases. The aim of this article is to review the current state of mRNA vaccine technology and its use against other diseases. **Methods:** To get accurate and reliable data, we carefully search the clinicaltrial.gov, and individual company's website for current ongoing clinical trials reports. Also, we accessed different NCBI databases for recent articles or reports of clinical trials, innovative design of mRNA vaccine and reviews. **Results:** Significant progress have been made in the design and improvement of mRNA vaccine technology. Currently, there are hundreds of ongoing clinical trials on mRNA vaccine against different cancer types, infectious diseases, and genetic and rare diseases which showcase the advancement in this technology and their potential therapeutic advantages over traditional vaccine platforms. Finally, we project what could be potential future direction in designing more effective mRNA vaccine, particularly against cancer. **Conclusions:** Results of many of the ongoing clinical trials have shown significant positive outcomes with many of the trials already at phase III. Despite this outlook however, some have been terminated or withdrawn for several reasons, some of which are not made available. This means that despite the advancement, there is need for more research and critical evaluation of each innovation to better understand their immunological benefits and long-term effects.

Keywords: mRNA vaccine; infectious diseases; cancer; personalized medicine; rare and genetic diseases; dendritic cells; lipid nanoparticles; exosomes

1. Introduction

The first mRNA therapeutic attempt was designed in 1995 to target cancer, loading the protein on dendritic cells (DCs) [1,2]. After this breakthrough research by Hsu and his colleagues, the technology of mRNA vaccine seemed to be in the shadow until the emergence of COVID-19 pandemic when mRNA vaccines were rolled out to tackle the diseases, which became the fastest vaccines to be approved during any pandemic in history. Despite this great success, the liquid nanoparticles (LNPs)-based mRNA vaccines were not without some drawbacks. Beside the need for storage and transportation under very low temperature, the associated cytokine storm that leads to many adverse immunologic effect have been reasons for serious concern [3,4]. Given their potentials however, many companies and institutions have been working to advance this technology and targeting other infectious and genetic diseases.

Some of the strategies to improve mRNA vaccines beside untranslated (UTR) and codon optimizations and nucleotide modification which were earlier used by many companies including Moderna and Pfizer in their vaccine designs, other recent approaches include, alternative delivery system such as polymer-based delivery system, exosome/peptide, ionizable lipid [5], and the use of next-generation lipid nanoparticles. Other advancements are the use of self-amplifying mRNA (sa-mRNA), thermostability, adjuvant integration, the design of personalized and targeted vaccine, and

the use of dendritic cell-based mRNA vaccines which seems to have gained more attention among other strategies [6–9].

Currently, numerous clinical trials are ongoing with the use of these innovative mRNA vaccines as therapies for infectious diseases such as influenza, rabies, Zika virus, Epstein-Barr Virus (EBV), Human Metapneumovirus (hMPV), Respiratory Syncytial Virus (RSV), Herpes Simplex Virus (HSV), and HIV (see Table 1). Available clinical trial data shows significant numbers of genetic and rare diseases are being investigated for potential cure using mRNA therapeutics, and different cancer types have also been targeted with mRNA vaccine formulations (see Table 2 and 3).

Table 1. Ongoing clinical trials on infectious diseases.

Company	Candidate	Product Type	Disease	Status	CT Ref
Sanofi	VAV00027	mRNA/LNP	RSV/hMPV	Phase I	NCT06237296
	VBS00001	mRNA vaccine	Pandemic flu H5	Phase I/II	NCT06727058
	MRT5421, MRT5424, and MRT5429	mRNA vaccine	Influenza	Phase I/II	NCT06361875
		mRNA vaccine	Influenza	Phase I/II	NCT06744205
	mRNA-NA	mRNA vaccine	Influenza	Phase I	NCT05426174
		mRNA vaccine	Influenza	Phase I	NCT05829356
		mRNA vaccine	Acne	Phase I/II	NCT06316297
	Rabipur® CV7202	mRNA vaccine	Rabies	Phase I	NCT03713086
	RNActive® CV7201	mRNA vaccine	Rabies	Phase I	NCT02241135
	MRT5413	mRNA vaccine	Influenza	Phase I/II	NCT05650554
		mRNA vaccine	Influenza	Phase I	NCT06118151
Moderna TX, Inc.	mRNA-1189	mRNA vaccine	Epstein-Barr Virus (EBV)	Phase I/II	NCT05164094
	mRNA-1644 mRNA-1574		HIV	Phase I/II	NCT03547245
	mRNA-1215		Nipah Virus (NiV)	Phase I	NCT05398796
	mRNA-1769		Mpox	Phase I/II	NCT05995275
	mRNA-1403		Novovirus/(Acute Gastroenteritis)		NCT06592794
	mRNA-1647		Cytomegalovirus (CMV)	Phase III	NCT05085366
	mRNA-1325, mRNA-1893	mRNA vaccine	Zika virus	Phase I Phase II	NCT03014089 NCT04064905

	mRNA-1010		Seasonal Flu	Phase III	NCT06602024
	mRNA-1011.1, mRNA-1011.2, mRNA-1012.1	Next-Gen mRNA vaccines	Influenza Virua	Phase I/II	NCT05827068
	mRNA-1345		Respiratory Syncytial Virus (RSV)	Phase III	NCT06067230
	mRNA-1365		Human Metapneumovirus (hMPV)	Phase I	NCT05743881
	mRNA-1608		Herpes Simplex Virus	Phase I/II	NCT06033261
	mRNA-1468		Herpes Zoster (HZ)	Phase I/II	NCT05701800
	VAL-339851		Seasonal influenza	Phase I	NCT03345043
	mRNA-1944		Chikungunya Virus	Phase I	NCT03829384
CanSino Biologics		mRNA vaccine	COVID-19	Phase I/II	NCT05373485 NCT05373472
National Institute of Allergy and Infectious Diseases (NIAID)	HVTN 302	BG505 MD39.3 mRNA/BG505 MD39.3 gp151 mRNA/BG505 MD39.3 gp151 CD4KO mRNA	HIV	Phase I	NCT05217641
	mRNA-1273	mRNA-LNP	COVID-19	Phase I	NCT04283461
	mRNA-1215	mRNA vaccine	Nipah Virus (NiV)	Phase I	NCT05398796
Massachusetts General Hospital		mRNA-transfected autologous dendritic cells	HIV-1	Phase I/II	NCT00833781
AstraZeneca	AZD9838/ AZD6563	mRNA-VLP	SARS-CoV-2	Phase I	NCT06147063
CSPC ZhongQi Pharmaceutical Technology Co., Ltd.	SYS6006	mRNA vaccine	SARS-CoV-2	Phase II	NCT05439824
Immorna Biotherapeutics, Inc.	JCXH-221	mRNA vaccine	COVID-19	Phase II	NCT05743335
	JCXH-108	mRNA vaccine	RSV	Phase I	NCT06564194
CNBG-Virogin Biotech (Shanghai) Ltd.	ZSVG-02-O	mRNA vaccine	COVID-19	Phase II	NCT06113731
Vaxart	VXA-CoV2-3.1	Oral SARS-CoV-2 Vaccine Tablet	COVID-19	Phase II	NCT06672055

Shenzhen Shenxin Biotechnology Co., Ltd	IN001	mRNA vaccine	Herpes Zoster	Phase I	NCT06375512
*** Lemonex	LEM-mR203	mRNA-DegradaBALL vaccine	COVID-19	Phase I	NCT06032000
Barinthus Biotherapeutics	ChAdOx1-HBV	mRNA HBV vaccine	Chronic HBV infection	Phase I	NCT04297917
RinuaGene Biotechnology Co., Ltd.	RG002	mRNA vaccine	HPV16/18 associated Cervical Intraepithelial Neoplasia Grade 2 or 3(CIN2/3).	Phase I/II	NCT06273553
Speransa Therapeutics		PRIME-2-CoV_Beta	COVID-19	Phase I	NCT05367843
Albert B. Sabin Vaccine Institute	Sinovac	mRNA vaccine	COVID-19	Phase IV	NCT05343871
Sinocelltech Ltd.	SCTV01E-2	mRNA vaccine	COVID-19	Phase II	NCT05933512
SK Bioscience Co., Ltd.	GBP560-A GBP560-B	mRNA vaccine	SK Japanese Encephalitis virus disease	Phase I/II	NCT06680128
Gritstone bio, Inc. Seqirus Stemirna Therapeutics	GRT-R912, GRT-R914, and GRT-R918	samRNA Vaccine	COVID-19/HIV	Phase I	NCT05435027
	V202_01	Sa-mRNA vaccine	Influenza	Phase I	NCT06028347
	SWC002	mRNA vaccine	COVID-19	Phase I/II	NCT05144139
	SW-BIC-213	mRNA vaccine	COVID-19	Phase III	NCT05580159
	SWIM816	mRNA vaccine	COVID-19	Phase II/III	NCT05911087

Table 2. List of ongoing clinical trials involving mRNA therapies for cancers.

Company	Candidate	Product Type	Cancer Type	Status	CT Ref
BioNTech	BNT111 TYR, vaccine, CTAG1B	mRNA vaccine	Malignant melanoma	Phase II	NCT04526892
	BNT113 vaccine	mRNA vaccine	Head and neck cancer	Phase II	NCT04534205
BioNTech/Regeneron Pharmaceuticals	BNT116 vaccine, TAA	mRNA vaccine	Non-small cell lung cancer (NSCLC)	Phase II	NCT05557591
BioNTech/Roche		mRNA vaccine	Malignant melanoma	Phase II	NCT03815058

	BNT112 (autogene cevumeran) vaccine, neoantigen		Colorectal cancer	Phase II	NCT04486378
			Other metastatic tumors	Phase II	NCT03289962
			Pancreatic ductal adenocarcinoma (PDAC)	Phase II	NCT05968326
			Muscle invasive urothelial carcinoma (MIUC)	Phase II	NCT06534983
		****	Metastatic castration resistance prostate cancer (mCRPC)	Phase I/II	NCT04382898
Moderna TX, Inc.	mRNA-4359 + pembrolizumab		Advanced solid tumors	Phase I/II	NCT05533697
	mRNA-4106 + Nivolumab/Relatlimab		Solid tumors	Phase I	NCT06880549
	mRNA-2752		Refractory solid tumors/lymphoma	Phase I	NCT03739931
	mRNA-2736		Relapsed/refractory multiple myeloma	Phase I	NCT05918250
Moderna/ Merck & Co	mRNA-4157 vaccine/ neoantigen	mRNA vaccine	Bladder cancer	Phase I/II	NCT06305767
			non-small cell lung cancer (NSCLC)	Phase III	NCT06077760
			Renal cell carcinoma	Phase II	NCT06307431
			Malignant melanoma	Phase III	NCT05933357
			Others	Phase II/III	NCT06295809
Stemirna		mRNA vaccine	Advanced malignant solid tumors	Preclinical	NCT05949775
			Personalized tumor vaccine for esophageal and non-small cells lung cancers	Preclinical	NCT03908671

CureVac	CV09050101	mRNA vaccine (CVGBM)	Glioblastoma (GBM)	Phase I	NCT0593838 Z
Fudan University	PANC-IIT-RGL-mRNA vaccine	mRNA vaccine	Pancreatic adenocarcinoma	Preclinical/phase I	NCT0615626 Z
	HRXG-K-1939	mRNA vaccine + adebrelimab	Advanced solid tumors	Phase I	NCT0594237 8
Guangzhou Medical University	ZZVACCINE-mRNA-020	Neoantigen mRNA vaccine	Advanced Solid Tumors	Phase I	NCT0619538 4
National cancer institute ***	NCI-4650	mRNA-based personalized vaccine	Metastatic epithelial cancer	Phase I/II	NCT0348015 2
Ruijin Hospital	Xp-004	mRNA tumor vaccine	Recurrent pancreatic cancer	Phase I	NCT0649637 3
	WGc-043	EBV mRNA vaccine	Refractory Lymphoma	Phase I	NCT0678860 0
Guangdong Provincial People's Hospital		Neoantigen mRNA vaccine	non-small cell lung cancer (NSCLC).	Phase I	NCT0673550 8
University Hospital Tuebingen	RNA-Mel-03	mRNA vaccine coding for Melan-A, Mage-A1, Mage-A3, Survivin, GP100 and Tyrosinase	Malignant melanoma	Phase I/II	NCT0020451 6
Shanghai Zhongshan Hospital		Personalized mRNA vaccine	Postoperative hepatocellular carcinoma	Preclinical	NCT0576171 Z
Steinar Aamdal***	DC-004	mRNA vaccine with dendritic cells	Metastatic malignant melanoma	Phase I/II	NCT0096184 4

Radboud University Medical Center		TLR-DC and Trimix DC loaded with mRNA encoding melanoma-associated tumor antigens (gp100 and tyrosinase)	Metastatic melanoma	Phase I/II	NCT01530698
*** Memorial Sloan Kettering Cancer Center		Vaccination With CT7, MAGE-A3, and WT1 mRNA-electroporated Autologous Langerhans-type Dendritic Cells as Consolidation	Multiple myeloma	Phase I	NCT01995708
		Autologous Langerhans-type Dendritic Cells with mRNA encoding tumor antigen	Melanoma	Phase I	NCT01456104
Shanghai Jiao Tong University School of Medicine	mRNA-0523-L001	Individualized mRNA neoantigen vaccine	Advanced endocrine tumor	Phase I	NCT06141362
John Sampson, Duke University	BTSC mRNA-loaded DCs	Personalized cancer vaccine	glioblastoma multiforme (GBM)	Phase I	NCT00890032
Sir Run Run Shaw Hospital	iNeo-Vac-R01	Personalized mRNA vaccine	Advanced Digestive System Neoplasms	Phase I	NCT06019702

		iNeo-Vac-R01 + standard adjuvant therapy			NCT0602677 <u>4</u>
Inge Marie Svane, Herlev Hospital		mRNA transfected dendritic cell	Metastatic prostate cancer	Phase II	NCT0144673 <u>1</u>
Steinar Aamdal, Oslo University Hospital ***	DC-004 **	mRNA vaccine therapy with dendritic cells	Metastatic malignant melanoma	Phase I/II	NCT0096184 <u>4</u>
	DC-006 **	Dendritic cells with amplified ovarian cancer stem cell vaccine	Recurrent Platinum Sensitive Epithelial Ovarian cancer	Phase I/II	NCT0133404 <u>7</u>
	DC-005	Dendritic cells with cancer mRNA vaccine	Prostate cancer	Phase I/II	NCT0119762 <u>5</u>
	DC-CAST-GMB	Dendritic cells with cancer mRNA vaccine	glioblastoma	Phase I/II	NCT0084645 <u>6</u>
Nanjing Tianyinshan Hospital	RGL-270	MRNA Vaccine + Adebrelima b	Non-small cells lung cancer	Phase I	NCT0668565 <u>3</u>
Radboud University Medical Center	TLR-DC and Trimix DC	Autologous dendritic cell vaccine	Melanoma	Phase I/II	NCT0153069 <u>8</u>
		mRNA vaccine	Melanoma stage III/IV	Phase I/II	NCT0024352 <u>9</u>
		MiHA-loaded PD-L-silenced DC vaccine	Hematological malignancies	Phase I/II	NCT0252868 <u>2</u>
		CEA-loaded dendritic cell vaccine	Colorectal cancer	Phase I/II	NCT0022818 <u>9</u>

***Ludwig Institute for Cancer Research	BI 1361849	mRNA vaccine + durvalumab + tremelimumab	Metastatic non- small cells lung cancer	Phase I/II	NCT0316477 <u>2</u>
YueJuan Cheng, Peking Union Medical College Hospital	KY- 1007	Personalized mRNA neoantigen vaccine	Advanced solid tumors	Early phase I	NCT0535935 <u>4</u>
Guangdong 999 Brain Hospital	PERCELLVAC3	Personalized cellular vaccine	Glioblastoma	Phase I	NCT0280841 <u>6</u>
	PerCellVac2	Personalized cellular vaccine	Glioblastoma	Phase I	NCT0280836 <u>4</u>
Jinling Hospital, China	SJ-Neo006	Camrelizumab + personalized neoantigen vaccines	Pancreatic cancer	Early phase I	NCT0632673 <u>6</u>
Wu Wenming, Peking Union Medical College Hospital	XH001	Neoantigen cancer vaccine + Ipilimumab	Pancreatic cancer	Early phase I	NCT0635364 <u>6</u>
University of Florida ***	RNA PRIME	pp65 RNA LP (DP1 & DP2) vaccines	Pediatric Recurrent Intracranial malignancies	Phase I/II	NCT0566040 <u>8</u>
	pp65 RNA-LP	mRNA vaccine	Recurrent glioblastoma	Phase I	NCT0638959 <u>1</u>
	PNOC020	RNA-loaded lipid particle (RNA-LP) vaccine	Pediatric High- Grade Gliomas (pHGG), and Adult Glioblastoma	Phase I/II	NCT0457314 <u>0</u>
	pp65-shLAMP ***	pp65-shLAMP mRNA DCs with GM-CSF	Glioblastoma Multiforme	Phase II	NCT0246526 <u>8</u>

Jianming Xu, The Affiliated Hospital of the Chinese Academy of Military Medical Sciences		mRNA neoantigen tumor vaccine	Advanced gastric, esophageal, and liver cancers	Early phase I	NCT05192460
	XH001	Neoantigen tumor vaccine, XH001 + sintilimab	Advanced solid tumors	Preclinical	NCT05940181
RinuaGene Biotechnology Co., Ltd.	RG002	mRNA therapeutic vaccine	HPV16/18 associated Cervical Intraepithelial neoplasia	Phase I/II	NCT06273553
Gary Archer Ph.D., Duke University		Dendritic cell-based mRNA vaccine	Brain tumor	Phase I	NCT00639632
		DC-based mRNA vaccine + Nivolumab	Brain tumors	Phase I	NCT02529072
University Medical Center Groningen	W_ova1 vaccine	Liposome formulated mRNA vaccine	Ovarian cancer	Phase I	NCT04163094
Zwi Berneman, University Hospital, Antwerp	CCRG12-001	DC vaccine	Acute myeloid leukemia (AML)	Phase II	NCT01686334
Svein Dueland, Oslo University Hospital		mRNA vaccine	Malignant melanoma	Phase I/II	NCT01278940
		mRNA vaccine	Androgen Resistant Metastatic Prostate cancer	Phase I/II	NCT01278914
Inge Marie Svane, Herlev Hospital		DC vaccine	Breast cancer	Phase I	NCT00978913
Peking Union Medical College Hospital	ABOR2014(IPM511)	Neoantigen mRNA vaccine	Advanced hepatocellular carcinoma	Preclinical	NCT05981066

Diakonos Oncology Cooperation	DOC1021	Dendritic cell-based mRNA vaccine loaded with tumor lysate	Adult Glioblastoma	Phase II	NCT0680530 5
Peking University Hospital & Institute	JCXH-212	Tumor neoantigen mRNA vaccine	Malignant solid tumors	Early phase I	NCT0557927 5
*** Merck Sharp & Dohme LLC	mRNA 5679/V941	mRNA vaccine	Metastatic Non-Small Cell Lung Cancer, Colorectal or Pancreatic Adenocarcinoma	Phase I	NCT0394876 3
University Hospital, Antwerp	CCRG 05-001	Dendritic-based mRNA vaccine	Acute Myeloid Leukemia	Phase I	NCT0083400 2
		DC vaccine	Pediatric High Grade Gliomas, and Diffuse Intrinsic Pontine Gliomas	Phase I/II	NCT0491162 1
The Affiliated Hospital Of Guizhou Medical University	InnoPCV	mRNA vaccine	Advanced solid tumors	Early phase I	NCT0649701 0

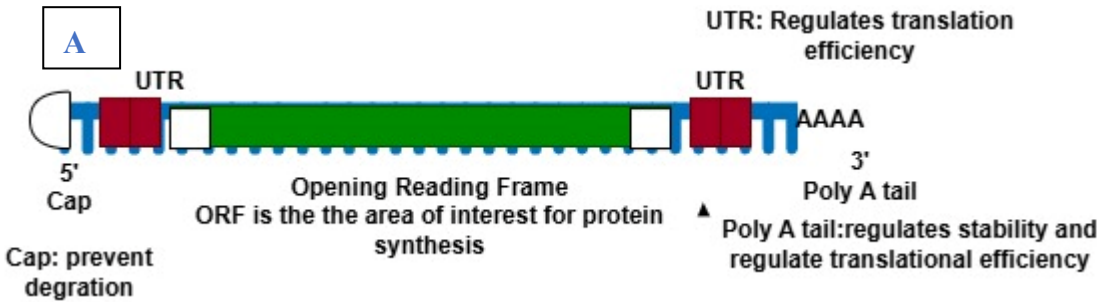
Table 3. multivalent vaccines in trials.

Company/sponsor	Candidate	Product Type	Disease(s)	Status	Reference
Duke University					
BioNTech/Roche	BNT112 (autogene cevumeran) vaccine, neoantigen	mRNA vaccine	Malignant melanoma	Phase II	NCT03815058
			Colorectal cancer	Phase II	NCT04486378
			Other metastatic tumors	Phase II	NCT03289962
			Pancreatic ductal adenocarcinoma (PDAC)	Phase II	NCT05968326
			Muscle invasive urothelial carcinoma (MIUC)	Phase II	NCT06534983
Moderna/ Merck & Co	mRNA-4157 vaccine/ neoantigen	mRNA vaccine	Bladder cancer	Phase I/II	NCT06305767
			non-small cell lung cancer (NSCLC)	Phase III	NCT06077760
			Renal cell carcinoma	Phase II	NCT06307431
			Malignant melanoma	Phase III	NCT05933577

			Others	Phase II/III	NCT06295809
	mRNA-1195	mRNA vaccine	Multiple Sclerosis	Phase II	NCT06735248
	mRNA-3927		Propionic Acidemia	Phase I/II	NCT04159103
	mRNA-3745		Glycogen Storage Disease Type 1a (GSD1a)	Phase I/II	NCT05095727
	mRNA-3705		methylmalonic acidemia (MMA)	Phase I/II	NCT05295433
	mRNA-1083		COVID-19 + Influenza	Phase III	NCT06694389
	mRNA-1975, mRNA-1982		Lyme Disease	Phase I/II	NCT05975099
	mRNA-1653		hMPV + Parainfluenza Virus Type 3 (PIV3)	Phase I	NCT04144348
	mRNA-1045		Influenza + RSV	Phase I	NCT05585632
	mRNA-1230		Influenza + RSV + SARS-CoV-2	Phase I	NCT05585632

2.1. The Structure and Mechanism of Action of mRNA Vaccines

mRNA vaccines contain synthetic mRNA molecules that direct the production of antigens to elicit immune responses. Structurally, the Invitro transcribed mRNA mimics the endogenous mRNA. The two main mRNA types under investigation as vaccine antigens are self-amplifying RNA and non-replicating mRNA [10]. The non-replicating (conventional) mRNA contains five components: 5' cap, 5' untranslated regions (UTR), an open reading frame (ORF), 3' UTR, and 3' end poly(A) tail. The self-amplifying mRNA contains all these components with an extra coding region in their ORF that codes for the viral replication machinery, allowing for continuous intracellular RNA amplification and subsequent increased antigen production[11]. The 5'cap contains 7-methylguanosine nucleoside (m7G) linked to the 5'-triphosphate bridge. The cap increases the stability of mRNA against 5' exonucleolytic degradation. Next to the 5'cap, the 5' UTR contains important regulatory areas such as the internal ribosome entry site (IRES) and ribosome binding site (RBS). These components recruit the ribosome and other translation factors to initiate and regulate translation. The open reading frame is the most important part of the vaccine as it codes for the area that is translated into the protein. The overall translation efficiency of mRNA can be maximized by selecting the right codons in this region. This can be done by replacing rarely used codons with more frequently occurring codons that encode the same amino acid residue[12,13]. The polyadenylated tail at the 3' end regulates the stability and translation efficiency of the mRNA by interacting with proteins that control its degradation and translation initiation (see Figure 1). Modified nucleosides are added to enhance translation. This modification prevents recognition by the antigen-presenting cells, leading to a high level of translation and producing a significant number of needed proteins/antigens (Jain *et al.*, 2021). The mRNA is encapsulated with lipid nanoparticles for efficient delivery into the cells.



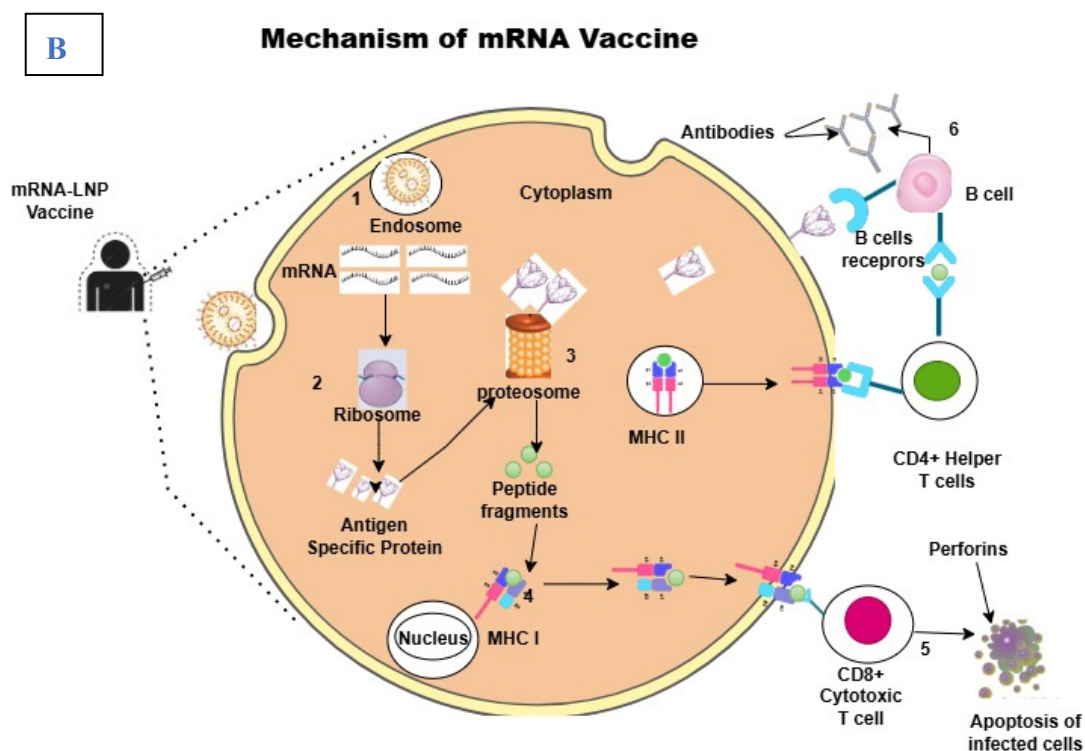


Figure 1. (A), an illustration of mRNA structure. B: the mechanism of mRNA vaccine in vivo. 1. After injection, the LNP encapsulated vaccine is internalized by APCs like dendritic cells and macrophages through endocytosis. 2, in the cytoplasm, the mRNA is released to be translated into tumor-specific antigen in the ribosome. 3, the synthesized antigens are processed into peptide fragment by proteasome. 4, the peptide fragments are loaded on major histocompatibility complex (MHC) molecules. MCH class I molecules present the peptides to CD8+ cytotoxic T cell, while MHC class II molecules present them to CD4+ helper T cells. 5, the interactions between MHC-antigen complexes and T cell receptors (TCRs) activates T cell which target and destroy tumor cells expressing the same antigen. The MHC II-antigen complex activates helper T cells which in turn activates B cell. 6, the interaction between helper T cell activates B cell for antibodies production and/or the B cell recognizes tumor-specific antigen on cell surface and form a complex via B cell receptors (BCRs) to activate B cells and lead to production of antibodies.

Upon injection of the vaccine, the muscular cells take up the LNP-mRNA. It escapes the endosome, releasing the mRNA into the cytoplasm[14]. Following its release, the host ribosome recognizes it and is translated into protein/antigen. The protein can be cleaved by the proteasome into peptides or transported outside the cell by the Golgi apparatus[15]. The danger-associated signals produced by the LNP recruit antigen-presenting cells like dendritic cells and neutrophils, which present the peptides to cytotoxic T lymphocytes on the cell surface by the major histocompatibility complex (MHC) class I. MHC class II proteins can also convey released antigens on the cell surface to helper T lymphocytes after they have been absorbed by cells and broken down inside endosomes[16,17]. As a result, CD8T cells generate humoral immunity that can neutralize subsequent infections from the same pathogen and establish a rapid immune response. Antigen-specific antibodies are produced by B cells and are triggered by either direct antigen recognition at the B cell receptor (BCR) or CD4T cell assistance[13,18]. Later, these antibodies can identify the same antigen in subsequent exposures, quickly triggering an immune response that prevents infection and growth. It is this humoral defense that brings long-term vaccine-mediated immunity.

2.3. Key Advantages over Traditional Vaccine Platforms

Unlike conventional vaccines (inactivated, live-attenuated, subunit, recombinant, and other conjugate types), mRNA vaccines offer several distinct advantages. First, the mRNA vaccine does not

contain the pathogen itself. Hence, there is no chance of infection after vaccination. The cell-free *In vitro* production also reduces safety issues such as viral contamination and cell-derived impurities commonly present in other platforms[19]. Second, since mRNA expression does not require nuclear entrance, it is safer than DNA-based vaccines and has a nearly minimal chance of random genome integration[20]. Third, its ability to encode several distinct antigens in a single formulation enables accurate and strong immune responses. It promotes humoral and cellular immune responses and induces the innate immune system. Fourth, the mRNA vaccine platform's adaptability is particularly beneficial for manufacturing since it allows for standardization of production, as changes to the encoded antigen do not affect the physical-chemical properties of the mRNA backbone (Armbruster *et al.*, 2019). Fifth, it has a wide range of applications. mRNA technology treats infectious diseases, genetic diseases, cancer, and diabetes. Lastly, mRNA is transiently active; hence, it is readily degraded by the metabolic pathways[21].

3. Applications Beyond COVID-19

3.1. Infectious Diseases

Infectious diseases remain a significant global threat to human health, particularly in low-income countries where emerging pathogens exist without approved vaccines or widely available treatments, resulting in devastating consequences[32,33]. The ongoing burden of infectious diseases on both health and the economy has been a persistent concern, driving extensive research in vaccine development[34,35]. Given that vaccines are a powerful means of enhancing global health security, several have been created to combat the threat of infectious diseases, significantly transforming disease prevention strategies[35–37]. With reduced concerns regarding insertional mutagenesis[11,19], remarkable progress has been made in applying mRNA technology for both infectious and non-infectious diseases. This technology has proven effective in treating cancer and infectious diseases[38]. The therapeutic and preventive roles of mRNA technology have been explored to support the treatment of infectious diseases. Recent advancements in mRNA design, delivery systems, and production scalability have expanded its applications to oncology, autoimmune disorders, and genetic diseases. The emergence of the COVID-19 pandemic has accelerated research into mRNA vaccines for other infectious diseases, highlighting their potential as a groundbreaking platform for vaccine development. This progress is particularly evident in the enhancement of delivery systems for these vaccines[33,36,39,40]. mRNA vaccines hold promising applications for various human infectious diseases caused by pathogens such as filoviruses (including Ebola), arboviruses (like Zika, Dengue, and Chikungunya), influenza, HIV, and rabies. Recent studies have underscored the potential of mRNA vaccines against the Zika virus (ZIKV). Starting with the first-generation mRNA-1325 Zika vaccine developed by Moderna, which is based on structural proteins from a 2007 Micronesia Zika virus isolate to the triple repeat domain III mRNA vaccine, 3xEIII, encapsulated in lipid nanoparticles (LNPs), both elicited neutralizing antibodies and long-term immunity in mice[27]. Similarly, other Zika virus vaccines, including the mRNA vaccine encoding ZIKV prM-E proteins in LNPs, provided protection in AG129 mice against lethal ZIKV challenges[41]. A self-replicating mRNA vaccine encoding ZIKV prM-E proteins demonstrated efficacy in IFNAR1-/- C57BL/6 mice. However, its effectiveness was inversely related to the dose in wild-type mice due to type I interferon responses[42]. An optimized mRNA vaccine, mRNA-1893, produced comparable neutralizing antibody titers to its predecessor at a lower dose, ensuring complete protection in non-human primates[43]. The HIV vaccine development has faced extreme difficulties consequent to the challenge of the high variability of the viral envelope antigens of HIV, driving the huge genetic diversity of HIV, and the frequent escape mutations consistent with the virus[44,45]. The fact that most people infected with HIV are infected with about 20% of HIV variants further compounds the problem of successfully developing a vaccine with broad neutralising antibodies (bNAbs)[46–48]. COVID-19 mRNA vaccine success has propelled numerous research and approaches in HIV mRNA development. Presently, the HIV-1 trimeric envelope (Env) glycoprotein

(gp160/gp140) has been targeted by mRNA-1574 Moderna as a vaccine candidate, while the engineered gp120 (outer domain of Env) and stabilised HIV-1 Env gp140 trimer developed by the eOD-GT8 60mer mRNA (IAVI/Moderna) and BG505 MD39.3 mRNA (NIH/NIAID) respectively[49–51]. Currently, the HIV mRNA vaccines are being tested in healthy individuals and HIV-infected patients with the aim of passive immunisation (*HIV mRNA Vaccine | List Results | ClinicalTrials.Gov, n.d.*).

The human avian influenza (H5N1) virus has been reported in more than 23 countries since its first report and has remained a significant threat to global health, resulting in continuous seasonal economic loss. Global yearly seasonal influenza epidemics record about 3 million people developing illnesses, of which up to 600,000 died (majorly children) from influenza cases worldwide[52,53]. For a long time, embryonated chicken eggs have been the platform for the generation of influenza vaccines, although this approach presented greater scalability, effectiveness was about 60% due to the constantly changing antigenic drift and shift, limited duration of immunity, and antigenic mismatch between the selected vaccine strains and circulating influenza strains[54] since influenza mutation is seasonally influenced[55], posing a challenge for the development of a global influenza vaccine. Although the mRNA influenza vaccine targeting Hemagglutinin (HA) has long been reported[56], the most significant mRNA vaccines for influenza came after the success of the mRNA vaccine for the COVID-19 pandemic. The trivalent mRNA vaccine candidate with cross-specific humoral immune response in mice was reported by Elena et al [57]. Others in clinical trials include the ARCT-2304 encoding viral glycoproteins (HA and neuraminidase) and the mRNA-1018 mRNA vaccine developed by Arcturus Therapeutics and Moderna, respectively [58]. The recent outbreak of influenza in the US has prompted the US Department of Health and Human Services (HHS) to announce £590 million in support of Moderna to expedite the development of mRNA vaccines against potential pandemic flu viruses[58,59].

3.2. Cancer Immunology

A recent publication by Chen et al (2023) estimated the global economic cost of cancers to be at \$25.2 trillion from 2020 to 2050, imposing a marked toll on the economy through reduced productivity, unemployment, labour losses, and capital investment reductions. Cancer treatments, including surgery, chemotherapy, radiation, and targeted therapies, have significantly improved patient outcomes in recent decades, but all these methods have come with limited outcomes[27,60], requiring a dire need for the alternative best option. Cancer immunotherapy's desired outcome is to achieve long-lasting positive responses in patients, therefore, the quest to develop effective vaccines and therapy for cancer treatment has advanced lately with the introduction of several technologies and approaches in therapeutics[27,60,61]. Cancer vaccines target treatment rather than prevention, unlike vaccines for infectious diseases. Their goal is to stimulate the patient's immune system using tumour antigens, triggering an antitumor response to help eliminate the tumour [62]. The successes of mRNA technology during COVID-19 revolutionised vaccinology and paved the way for numerous breakthroughs in disease treatment, particularly in cancer. The uniqueness of mRNA technology for cancer therapy includes the versatility and flexibility of mRNA to encode multiple antigens against diverse tumour-associated antigens (TAA), the ability to induce both humoral and cellular immune responses, leading to broader and more robust protection against cancer in terms of vaccine, the use of mRNA to encode tumour-specific antigens (TSA) allows the immune system to recognise and eliminate cancer cells displaying these antigens[27]. mRNA therapy offers numerous advantages over traditional cancer immunotherapy, primarily its ability to be used to achieve both monotherapy and synergistic effect for cancer immunotherapy, addressing the known features of tumour immune evasion and resistance, limited response rate and specificity, immune-related adverse effects [61,63]. Issues of safety, delivery methods and personalised treatments are addressed in most mRNA candidates for cancer immunotherapy[60]. Despite its advantage in inducing cross-presentation of multiple epitopes in antigen-presenting cells (APCs) with patient-specific human leukocyte antigens (HLA), reducing HLA type restrictions and boosting T cell responses, a lot of research is still required

in personalised mRNA cancer vaccines. Numerous mRNA cancer vaccines are currently in clinical trials, ranging from ex vivo mRNA-based DC vaccines to in vivo mRNA cancer vaccines. Promising results from clinical trials, such as the Lipo-MERIT trial, have demonstrated the effects of mRNA vaccines targeting melanoma-associated antigens, resulting in long-lasting immune responses in patients with advanced melanoma [64]. The Phase 3 clinical study of Adjuvant V940 (mRNA-4157) with Pembrolizumab shows promising results as a personalized cancer vaccine targeting tumour neoantigens in high-risk stage II-IV melanoma patients. This treatment significantly prolongs recurrence-free survival (RFS) and reduces the risk of recurrence or death by 44% [60,65].

Prostate cancer is the leading cancer among men in sub-Saharan Africa, with increasing incidence rates and high mortality rates [66]. Recent immunotherapies target either key tumour-associated antigens (TAA) or tumour-specific antigens (TSA). Tumour-associated antigens (TAA) are the most common prostate cancer antigens. They are characterized by weak tumour immunogenicity and specificity. To address this issue, mixtures of TAAs are being utilized to enhance the efficacy of cancer vaccines [67]. TAA serves as the target for the multivalent mRNA vaccine, CV9103 (CureVac), which encodes the PSA, PSCA, PSMA, and STEAP1 antigens for the treatment of patients with advanced prostate cancer [68]. In Phase I/IIa clinical study involving 44 patients with advanced castration-resistant prostate cancer (CRPC), CV9103 was well tolerated and immunogenic, leading to an enhanced version of the vaccine, CV9104, which includes prostatic acid phosphatase (PAP) and mucin 1 (MUC1). The RActive® prostate cancer vaccine CV9104 was evaluated in a randomised, placebo-controlled Phase II trial to determine its clinical efficacy in prolonging survival for patients with asymptomatic or minimally symptomatic castrate-resistant metastatic prostate cancer [69]. However, the trial was terminated because the results showed no recent updates indicating a significant difference in overall survival (OS) between the treatment and control groups [70].

3.3. Personalised Medicine

-Potential in creating individualised vaccines for patients based on genetic profiles

The Human Genome Project has set the foundation for personalised medicine by providing a comprehensive mapping of the human genome. This mapping illustrates that an individual possesses a unique genetic makeup, which is valuable information for disease prevention, prognosis, diagnosis, and treatment [71]. Personalised medicine, also known as "precision medicine," has revolutionised patient treatment by overcoming the limitations of conventional pharmacotherapies. [72]. In personalised medicine, individualised treatment can be designed based on the specific characteristics of the individual identified through genomic investigations, specifically pharmacogenetic therapies. Lately, cancer immunotherapy has harnessed the specific characteristics of each tumour, developing vaccines and treatments with personalised approaches. mRNA vaccines have become a groundbreaking technology in oncology and personalised medicine, showing great potential for treating cancer. Their quick production and adaptability significantly advance immunotherapy [73]. mRNA vaccines targeting either key tumour-associated antigens (TAA) or tumour-specific antigens (TSA) have been developed [70,74]. and have shown promising results. Tumour-specific antigens (TSA) or neoantigens provide a robust vaccination, providing better tumour specificity, and are not known to generate autoimmunity [75]. Because of their uniqueness and specificity to cancer cells, rationally, ongoing clinical trial outcomes have favoured more TSA vaccine development [60,76]. Most cancer mRNA personalised vaccines are TSA-based. TSA-based vaccines combine large-scale sequencing, bioinformatics algorithms, and patient immunology. Recently, Merck and Moderna developed an individualised neoantigen therapy (INT) approach for treating patients with resected high-risk melanoma with mRNA-4157 (V940) in combination with pembrolizumab [77]. This approach demonstrated clinically meaningful improvements in both recurrence-free survival and distant metastasis-free survival (62% reduction in the risks of distant metastasis and death) compared to pembrolizumab monotherapy, a contrast to the traditional checkpoint inhibitors with evidence of melanoma recurrence [77,78]. The mRNA-4157 (V940) is in a phase III clinical trial stage. BioNTech

recently published three-year follow-up data from a Phase 1 trial, which showed that 8 out of 16 patients exhibited sustained polyspecific T cell responses in patients with resected pancreatic ductal adenocarcinoma. This was associated with a delayed recurrence of tumours over three years following treatment with their mRNA (iNeST) or BNT122 vaccine, developed in collaboration with Genentech [79], encouraging the initiation of a phase II trial [74]. Furthermore, Gritstone Bio's neoantigen cancer vaccine GRANITE (GRT-C901/GRT-R902) phase 2/3 study indicates a potential for clinical benefits for colorectal cancers in combination with immune checkpoint inhibitors [80]. Other personalised mRNA vaccines, such as Frame Therapeutic FRAME-001, in a phase II trial for the treatment of III-IV non-small cell lung cancer [81]. Indeed, the emergence of mRNA vaccine technology represents a significant shift in personalised cancer immunotherapy. Continual advances in high-throughput sequencing, neoantigen prediction, and nanocarrier systems sustain this strategy. Also, combining these vaccines with immune checkpoint inhibitors enhances their efficacy against tumour immune evasion. As these technologies improve, pharmacogenomics is expected to become cost-effective and more practical, promoting wider adoption of precision immuno-oncology in the future.

4. Innovations in mRNA Vaccine Designs

The technology of mRNA therapeutics has been in existence over the past few decades, but not until during the COVID19 pandemic that its fame spread across after Pfizer and Moderna announced their mRNA vaccine for COVID-19. Stemirna Therapeutics is a mRNA-based technology company, established in 2016 to maximize the potential of RNA science. In spite of the successes recorded with the use of LNP for mRNA vaccine delivery during COVID19, the technology faces many limitations. They are sensitive to temperature fluctuations and require ultra-cold storage (between -20 to -80°C). Some LNP components can trigger innate immune responses leading to inflammation and adverse reactions. For a detailed review on current strategies to reduce the risks of mRNA vaccine toxicity, we recommend [82]. Following the development and successful delivery of mRNA COVID-19 vaccine using lipid nanoparticles (LNP), there have been several attempts to improve and to design new platforms that offers efficient and more targeted delivery of vaccines with reduced immune toxicity.

4.1. *Advances in Lipid Nanoparticle (LNP) Delivery Systems*

Lipid nanoparticles (LNP) are non-viral vectors that have gained wide application as efficient delivery tools. They have low cytotoxicity and immunogenicity, high tissue penetration, high nucleic acid encapsulation, and efficient transfection with good biocompatibility[22]. Structurally, LNP consists of phospholipids, cholesterol, and polyethylene glycol (PEG) containing lipids. Phospholipids improve stability, enhance ease of mRNA encapsulation, and promote cellular absorption. Ionizable lipids have unique pH-responsive qualities that allow them to become positively charged in acidic environments, like the endosomes, and stay neutral during systemic circulation [23]. They are neutral at physiological pH, encouraging stable LNP production, prolonging bloodstream circulation, and inhibiting immune cell clearance. In the acidic environment, they become protonated (positively charged) and directly interact with the negatively charged phospholipids, promoting the release of cargo into the cytoplasm and aiding in the rupture of the endosomal membrane. Cholesterol stabilizes LNP structure, regulates the fluidity and permeability of membranes, and improves particle stability[24,25].

Lipid nanoparticles are classified into four groups: liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and hybrid lipid-polymeric nanoparticles. Liposomes are the early version of LNPs. They contain a phospholipid bilayer, which is typically made of phosphatidylcholine (PC) or other phospholipids, which self-assemble into bilayers due to their amphiphilic nature, the aqueous core and hydrocarbon chain[2,26]. The aqueous interior of liposomes contains hydrophilic drugs, as the hydrocarbon chain portion of the lipid bilayer entraps hydrophobic drugs. Its size ranges between 20-1000nm. Liposomes can be synthesized as unilamellar

or multilamellar. Small Unilamellar Vesicles (SUVs): 20–100 nm consists of a single bilayer. Large Unilamellar Vesicles (LUVs): 100–500 nm, have a single bilayer but larger encapsulation volume. Multilamellar Vesicles (MLVs): 0.1–10 μm , composed of multiple concentric bilayers. The size determines the half-life and drug encapsulation of the liposome. The small unilamellar liposomes exhibit higher encapsulation efficiency, Increased drug half-life, and the ability to evade the immune system[27]. Liposomes are challenging to produce on a large scale, they require complex production using organic solvents. Solid and nanostructured lipid nanoparticles are produced to overcome these challenges.

SLNs are solid colloidal particles that range in size from 4 to 1000 nm. They contain physiological, biodegradable, and biocompatible lipids and surfactants in their formulation, which can incorporate both lipophilic and hydrophilic drugs inside the lipid matrix[24,28]. The solid lipid serves as the dispersed phase, while the surfactant acts as an emulsifier. The solid lipid is typically made from triglycerides, glyceride mixtures, or even waxes, and it stays solid at room and body temperature; the surfactant concentration range is usually 0.5 to 5% (w/v) to improve formulation stability[2,29]. The selection of lipids and surfactants significantly impacts the nanoparticle formulation's physicochemical properties. The structure of SLN is determined by the production method and the solubility of the component and component formulation. Three structural types have been described: the homogenous matrix model, the drug-enriched shell, and the drug-enriched core. A homogenous matrix model is used for highly lipophilic drugs, the particles are created using a cold or hot homogenization process. The drug is either dissolved in a lipid matrix, a high-pressure homogenization process, and mechanical breakings leading to nanoparticle formation, or the lipid is dissolved in a lipid matrix with increased temperatures, leading to nanoparticle formation. It offers slow and controlled drug release. The drug-enriched shell is produced by hot homogenization as the system cools down the lipid precipitate, forming the lipid core. The concentration of the drug increases until its solubility limit is reached. When this limit is reached, the mix of drug and melted lipid crystallizes to form an outer shell. It results in a faster release of drugs. In the drug-enriched core, the drug crystallizes before the lipid and gets trapped in the core, with a pure lipid shell forming around it. Occurs when the drug has higher solubility in the molten lipid but separates during solidification[25,29]. Unlike liposomes, SLNs have prolonged release and better stability. However, the solid lipid's crystalline structure causes its poor integration rate, and it tends to gelate. NLCs are developed to overcome the disadvantages of SLNs.

NLCs are modified forms of SLNs that contain a mixture of solid and liquid phases (oil), forming a formless matrix, improving stability and capacity loading[22,27,28]. The lipids used here are biologically compatible, hence reducing toxicity. Depending on their structure, they can be classified into three: The imperfect crystal type comprises lipids with different chain lengths forming a matrix with several voids and imperfections that provide a more suitable environment for drug incorporation. The amorphous type is obtained using medium chain-length triglycerides and solid lipids. The solid lipids do not undergo recrystallization, thus resulting in solid particles with an amorphous structure. The drug's unwanted release is reduced, extending its shelf life. The multiple LNC has nanocompartments of oil containing dissolved drugs[27,30,31].

Methods like high-pressure homogenization, ultrasonication, spraying drying, solvent injection, double emulsion, and microfluidics are used to prepare lipid nanoparticles. Microfluidic is the recent form that leads to the production of nanoparticles with uniform particles; it is a promising approach for the large-scale production of SLNs and NLCs[24,25].

4.2. Improvement in Delivery Systems

The FDA-approved COVID-19 vaccines (Pfizer-BioNTech and Moderna) utilized LNPs with proprietary lipids like ALC-0315 (Pfizer) and SM-102 (Moderna) [23]. These LNPs used ionizable lipids that self-assemble with mRNA at acidic pH which promotes endosomal escape. Beside LNP, platforms such as improved ionized lipids, polymer-based delivery systems, peptide-based delivery, and exosome and extracellular vesicle (EV) delivery are being investigated to bypass LNPs

limitations. A 2022 study conducted by Kamerker and her colleagues demonstrated engineered exosomes delivered mRNA to pancreatic cancer cells with higher efficiency [83].

While mRNA vaccine for COVID-19 remains one of the greatest achievements in modern medicine, the idea of using this concept for cancer started over 20 years ago when Hsu and his colleagues demonstrated for the first time, the potential of using autologous tumor-specific antigen loaded on dendritic cells to induce antitumor immune response in cancer patients[1]. This groundbreaking clinical trial of using DCs for vaccine in cancer, laid a crucial foundation for what has now become a golden approach, and many researchers now focused on the use of monocyte-derived DCs (moDC) generated in vitro for mRNA vaccine production. The efficacy of this type of DCs have led to the approval of Sipuleucel-T (a DC-based vaccine) for prostate cancer by the FDA. Recently, however, due to extensive culture periods and supplements required to produce mature moDCs, many researchers have sought for alternative ways of generating DCs. Myeloid DC (mDC) and plasmacytoid DC (pDC) are two alternatives that have shown promising immunologic and clinical outcomes in metastatic melanoma patients [7,9], and lung cancer [6]. pDCs have also been shown as promising tools for multispecific viral and tumor antigen-specific T cells [8]. For a comprehensive review on the use of dendritic-based vaccine in immunotherapy, we refer readers to a recent review on this subject [84]. Furthermore, to enhance targeted delivery, LNPs are now being conjugated with antibodies or peptides to enable cell-specific delivery. For example, targeting dendritic cells via CD40 ligands enhances antigen presentation, as shown in cancer vaccine trials [85]. Pulsing DCs with human cytomegalovirus (CMV) pp65-LAMP (lysosomal-associated membrane protein) mRNA to target gliomas is currently being investigated in the clinical trial ([NCT03688178](#)), and it will be interesting to know the outcome of the trial. This cytomegalovirus unique protein has been reported in significant amount of people suffering from malignant gliomas (MGs), and targeting the proteins within cancer microenvironment provide alternative therapeutic potential to gliomas and this approach might be relevant to other cancer types.

4.3. Strategies for Enhancing Stability and Immunogenicity

As already mentioned, one of the challenges of LNPs is the need for extremely low temperature for their storage and transportation. Hence, there is need for improved and higher storage condition.

The technology involved in the development of ARCT-154 (Kostaive) vaccine by CSL and Arcturus Therapeutics that was given approval in Japan includes addition of an active substance, zapomeran which is a self-amplifying messenger RNA (mRNA). This self-amplifying mRNA (also called sa-mRNA) has an instructional mechanism for making an enzyme replicase, which in turn helps to make additional copies of mRNA upon delivery. Unlike other approved COVID-19 vaccines, Kostaive can be kept at higher temperature of about 2°C. Furthermore, development of this sa-mRNA vaccine is reported to significantly reduce immunogenicity as low doses are required to stimulate potent cellular immune responses. This will effectively reduce immune toxicity and other adverse effect associated with other COVID-19 vaccine. Also, mRNA1283, a next-generation COVID vaccine developed by Moderna which is currently in phase 3 trial, and it can be kept at a temperature of about 2-5°C [86]. Also, addition of adjuvants to the mRNA vaccine is another notable innovation that would enhance vaccine's protection. Co-delivering immune stimulants (for example, TLR agonists) enhances will improve responses. BioNTech's FixVac platform incorporates uridine-rich mRNA to activate TLR7/8, boosting T-cell immunity in melanoma trials [64].

4.4. Multivalent Vaccine Designs for Multiple Pathogens or Cancer Antigens

Viruses are known for their unique ability to mutate rapidly. This variability within the same species of viruses reduces the ability of monovalent vaccines to protect against different serotypes of some viruses of global significance. The emergence of variants of concerns (VOCs) necessitates the proposal for booster doses for COVID-19 pandemic. Another example is influenza virus. One of the major challenges for the development of vaccine for influenza virus is the multiple subtypes with varying degree of mismatches. Following recent advances in nucleic acid-based vaccine however,

Arevalo and colleagues have developed a multivalent vaccine that encodes all the 20 known subtypes [87]. There are applications of this method also in cancer immunotherapy.

Currently, there are numerous ongoing clinical trials that are investigating the potential and immunogenic properties of several mRNA vaccines encoding tumor-specific neoantigen (see Table 2) to specific cancer. Personalized neoantigen vaccines (for example, BioNTech's BNT111) target patient-specific tumor mutations. A 2021 trial by Sahin et al. reported prolonged survival in melanoma patients [88].

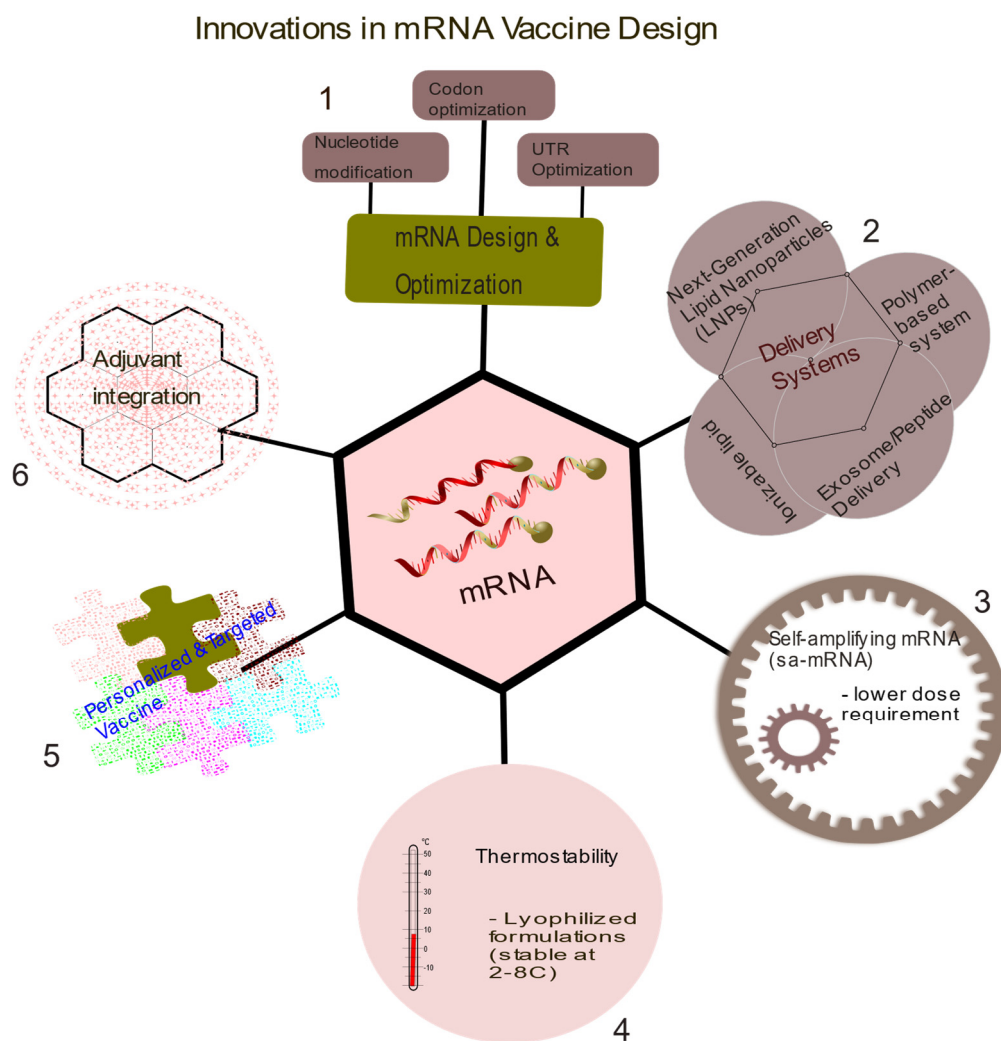


Figure 2. Summary of current innovations in mRNA vaccine design. 1. Structural optimization of mRNA to enhance packaging and delivery. 2. New methods aimed at improving delivery systems over the traditional lipid nanoparticles such as the use of exosome/peptide, ionizable lipids for easy processing and the release of mRNA molecules upon injection. 3. Self-amplifying mRNA (sa-mRNA) for lower dose requirement of mRNA vaccine as the incorporated molecules like zapomeran helps to produce more copies of mRNAs. 4. Thermostability is another strategy to overcome the need for low temperature for storage and transportation of mRNA-LNPs vaccines. These vaccines are stable at temperature of about 2-8°C. 5. Personalized and targeted vaccines based on patients' genetic profile. 6. Adjuvant integration of additional molecules like cytokines or combination of vaccine with traditional immune blockade therapies.

5. Current Challenges

5.1. Manufacturing and Scale-Up

- Challenges in production and supply chain scalability.

Over the last decade and a half period, mRNA vaccine development has undergone significant progress. The emergence of the Coronavirus disease 2019 (COVID-19) pandemic put the mRNA technology for vaccines to a test and this was a success story with the first production of mRNA vaccines in less than a year of the pandemic[89]. This has resulted in a significant reduction in the time of production, cost, and ease of vaccine production leading to a more rapid response to disease outbreaks as demonstrated during the COVID-19 pandemic. There have been efforts to improve the technology further as demand for mRNA vaccines continues to increase. Wei et al worked on the development of a universal integrated platform aimed at streamlining and enhancing on-demand preparation[90]. More advances in artificial intelligence have been propelling mRNA technology further, however, some challenges may persist especially with differential global capacity.

- Addressing regional manufacturing gaps.

Vaccine production capacity is limited in most LMICs, for example, there are 11 vaccine manufacturing facilities in Africa but their production capacities could hardly meet up to 1% vaccine for the over 50 countries of the continent. Significant deficiencies in infrastructure, technology, and human capital [91]. Conscious efforts and deliberate investment will be required to reverse this and the African Union (AU) should lead the continental efforts.

5.2. Cost and Accessibility

Generally, the production of mRNA vaccines has been documented to be cheaper when compared with traditional vaccine production. mRNA vaccines possess the advantage of fast manufacturing as short as half a year in contrast to the traditional method which may take 10-15 years. Notwithstanding these forgoing merits, the mRNA vaccine requires higher capital and starting materials. This becomes more significant in the low-and-middle-income countries that do not have adequate resources (material and human) to compete favorably with countries that are well-developed[92]. This challenge may further worsen the vaccine inequality that characterized COVID-19 vaccination at the peak of the pandemic between the global north and south. For example, Africa only supplies 1% of global vaccines [93]. The implication of this is that Africa which constitutes almost 20% of the world will have to continue to depend on other nations to meet its vaccine needs.

- High costs of mRNA technology compared to traditional vaccines.

There should be concerted efforts to ensure global vaccine equity. This could be led by the World Health Organization and other vaccine multinational groups like GAVI, the vaccine alliance. This may include but is not limited to technology transfer and license sharing. Health system strengthening and improvement is another important factor in vaccine equity especially in many low-and-middle-income countries[94].

- Strategies for reducing costs and ensuring global equity.

Global equity for vaccines is not just right but is in the best interest of global health. It is important to learn from the lesson of COVID-19 vaccine nationalism and other barriers to the equitable distribution of mRNA vaccines especially in LMIC. For example, local manufacturing of vaccines in Africa requires urgent attention and investment. Africa consumes one-quarter of the global vaccines but 99% of these vaccines are produced outside of the continent. Scaling up local capacities for vaccine manufacturing will reverse this. The steps to take will include technology

transfer, regulatory system strengthening, training, and workforce development [91]. In the long term, these efforts will drastically reduce the cost of vaccines and ensure global equity.

5.3. *Safety Concerns and Public Acceptance*

- Addressing adverse effects (e.g., myocarditis).

The novelty of SARS-CoV-2 at the start of COVID-19 led to many uncertainties not just about the virus but also about the introduction of the COVID-19 vaccine which was developed at an unprecedented speed of less than a year. The implementation and emergency authorization of the new technology of utilization of mRNA vaccine in humans for the first time raised many concerns. One such concern was the adverse events that could be associated with the new vaccines. While overall the mRNA vaccines for COVID-19 have been shown to be safe, there was a report of unusual adverse events. In a multinational study of over 99 million participants with combined doses of approximately 220 million of two COVID-19 mRNA vaccines (BNT162b2 and mRNA-1273), there was confirmation of pre-established safety signals relating to the cardiovascular system (myocarditis and pericarditis), neurological system (acute disseminated encephalomyelitis) and the identification of more safety signals including facial Bell's palsy, febrile and generalized seizure, idiopathic thrombocytopenia, cerebral venous sinus thrombosis, splanchnic vein thrombosis, and pulmonary embolism [95]. It is important to further assess these findings in association studies rather than observational cohorts and to determine the clinical significance and implications. In another trial setback, the FDA has put on hold all RSV vaccine trials in small children citing an increase in severe illness following the negative outcome of clinical trial conducted by Moderna among children aged 2-5 years old [96]. Furthermore, two clinical trials on DC-based mRNA vaccine for cancers were terminated by Oslo University Hospital. However, no information has been provided for these terminations.

- Public skepticism in the wake of misinformation.

The global mobilization of human and material resources to tackle the COVID-19 pandemic faced the challenge of misinformation and disinformation resulting in public skepticism, vaccine hesitancy, and anti-vaccine ideologies. Some of the related skepticism include mutation or genetic changes posed by the vaccines, induction of autism, the vaccines were chips, and that they could cause injury and death [97]. Social media were instrumental to the spread of misinformation and disinformation on the vaccines. The WHO and other global and local health authorities however rose to the occasion to address this challenge.

6. **Regulatory and Ethical Considerations**

- Regulatory landscape for mRNA vaccines beyond COVID.

The application of mRNA vaccines has expanded beyond their use in infectious diseases, there are various mRNA technology uses in immunotherapy and cancer. Regulatory oversight will be very critical to ensure consistent ethical application of the rapidly evolving technology. There are no formal regulatory guidelines that are specific to mRNA vaccines according to the World Health Organization although key regulations for manufacturing and quality control are in place. Similarly, no regulatory guideline exists in the European Union while the United Kingdom and United States regulation is based on the Human Medicines Regulation of 2012 and the Food and Drug Administration (FDA) respectively [98]. These are the same with regulatory bodies in other part of the world. This is an important gap that needs to be addressed and tackled on time.

- Ethical concerns related to personalized mRNA vaccines.

The application of personalized mRNA cancer vaccine is becoming a reality and the issue of associated issues such as cost and equitable access, data privacy, and potential unintended side effects especially in the long-term. The concern of vaccine nationalism as it was with the COVID-19 vaccine

may also resurface here [99]. The issue of technology transfer to LMIC given the enormous resources that are associated with the development of these vaccines. All these and other related matters will require attention.

7.0. Future Direction

The current trend of designing multivalent mRNA vaccines for infectious diseases is a laudable approach that will help to protect millions of people across the world. Considering the number of ongoing clinical trials involving the use of dendritic cell-based mRNA vaccine, especially against cancers, one other approach that will be worth exploring is to load tumor-specific neoantigen mRNA on multiple combined dendritic cells (for example pDC and mDC). This will most likely increase immunological response by activating more MHC molecules, and invariably, activation of cytotoxic T cells to target cancer cells (see Figure 3). Beside activating MHC I and II, DCs can provide signals for co-stimulatory molecules and cytokine secretion ensuring specific T cell activation[100]. Moreover, these DCs are considered to be relatively easy to propagate ex vivo. One important tool that will be valuable in the design of more targeted and personalized mRNA vaccine is the use of AI.

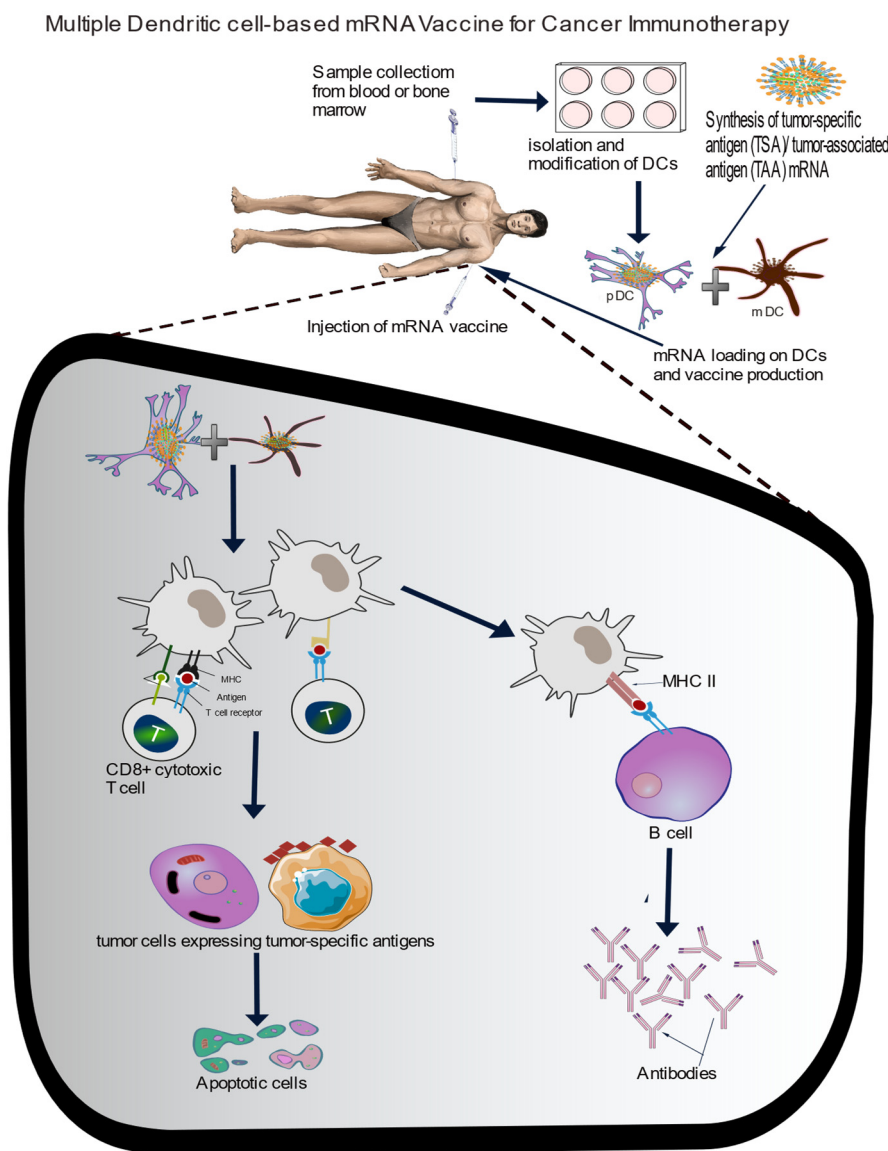


Figure 3. scheme for multiple dendritic cell-based mRNA vaccine against cancers. The combination of myeloid DC (mDC) and plasmacytoid DC (pDC) could significantly improve immune activation and antibodies production against cancer.

8.0. Conclusion

It is encouraging to see the level of progress that have been made over the past few years since the emergence of mRNA vaccine. Despite public skepticism, the available clinical trials data reveal a profound justification for continuous research and collaboration to addressing global health challenges. With increasing number of clinical trials in the use of mRNA vaccines, particularly, not just against infectious diseases but also cancer, this technology will usher in a new era in vaccinology. The collaboration between companies to optimize different structural components of the vaccine should be replicated among universities and institutions' mRNA experts in order to overcome current challenges facing this area of research. Finally, it would be desirable to see more funding support from government and all stakeholders to ensure equity and global distribution of this technology to people who need them the most.

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