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ACHIEVEMENTS AND DIFFICULTIES IN THE DEVELOPMENT OF mRNA VACCINES AGAINST INFECTIOUS AND CARCINOGENIC DISEASES

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ABSTRACT: Nowadays, in the time of scientific technology, mRNA vaccines have become a promising technology stage for the revolution of vaccines. Since mRNA vaccines provide a flexible and quick method of battling infectious diseases and cancers brought on by viruses, they have significantly changed the field of vaccination. Studies have shown that mRNA vaccines can prevent COVID-19 with efficacy rates between 94% and 95%, and their potential as a potent vaccine platform is becoming more widely acknowledged. Despite being crucial in combating the pandemic of COVID-19, mRNA vaccines still have a number of drawbacks. These include their instability and disintegration, which impairs their capacity to be stored, administered, and used effectively overall. Due to its instability and negative charge, mRNA is usually encased in a procedure of transport to facilitate approaching the target cell. When mRNA is administered via lipid-nanoparticle-based vaccine delivery systems (LNPs), for example, it only enters cells to make

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an endosome by endocytosis without damaging the cell membrane. The pandemic of COVID-19 has accelerated the progression of platforms of mRNA vaccines, which are employed in the management and prophylaxis of several infectious ailments. The main objective of this research is to introduce several possible uses for mRNA vaccine technology, which could result in the creation of a desired vaccine design. Consequently, the general public has been able to obtain and become more familiar with a new generation of immunizations. mRNA vaccines can be used to modify the structure of an antigen in response to novel modifications in the viral genome and even to merge sequences from distinct versions. The security and defence offered by recent mRNA vaccinations are sufficient, but it will take more clinical research to ascertain how long those benefits will last.

KEYWORDS: mRNA technology, vaccine research, infectious disorders, and malignancies caused by viruses

INTRODUCTION

Conventional vaccination methods have advanced, yet problems still exist, which has led to the development of novel vaccine technologies [1]. Epidemic outbreaks are caused by biological infections, and they happen almost annually. These epidemics always start off abruptly, are very contagious, spread swiftly, and have a detrimental effect on society [2]. The ideal setup would involve a "vaccine on demand" strategy that facilitates rapid inoculation expansion, mass manufacture, and delivery. Such a strategy would not work with the vaccination technology platforms that are now in use, which often call for labor- and time-intensive research and development processes [3]. Vaccinations based on nucleic acid structure, such as virus-related directions and mRNA, which become useful for getting speedy responses because of their capacity to trigger widely protective immune responses and their flexibility in synthesis [4]. By employing identical production accommodations, invention processes, and distillation procedures for all types of vaccines that are constructed on the same type of nucleic acid, vaccine production can be finished more swiftly and economically [5]. Nucleic acid-based vaccinations can be made without the need for encoded antigens, making this practicable. Vaccines based on nucleic acids induce cytotoxic T cells and humoral reactions resulting from immunization because they replicate an infection caused by a virus to generate antigens of the vaccine in situ [6]. This benefit is crucial

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for effectively eliminating intracellular infections or illnesses, as these require robust humoral and cellular immune responses. mRNA-based vaccines are more advantageous than vaccines utilizing viral vectors in terms of dosage [7]. Vaccines of mRNA that are not bound for requirements of packing and are capable of producing antigens of complex type, which further can be applied for accomplishing antigens in situ invention having no need to breach the membrane of the nucleus, which acts as a barrier for protein expression [8]. It is not the only problem that can alter the cell's DNA or infectious particle synthesis. Once the sequence of a gene is known, vaccines of mRNA can be prepared quickly within a short time frame by using pure methods of synthesis. Due to the availability and versatility of broad-ranged targets, the platform of mRNA is ideal for rapid responses [9].

Advances in mRNA Technology for Research on Vaccines Against Other Diseases, Viral Infections, and Mutation-Induced Cancers

It has taken years of preparation and study to produce mRNA vaccines in an efficient manner. Although the mRNA molecule was first described by Brenner and colleagues in 1961, it wasn't until 1969 that the first protein was made in vitro from extracted mRNA due to the extraordinary fragility of the mRNA molecule [10]. Since their initial proposal by Wolff et al. (1990), mRNA vaccines have been developed over the previous thirty years [11].

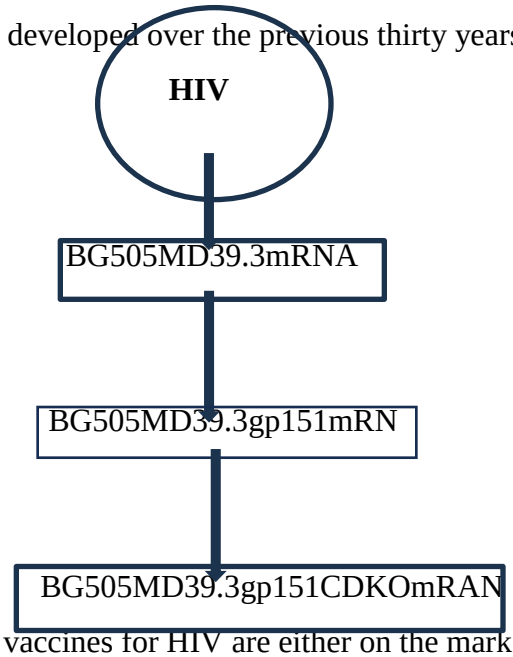

Figure 1. the number of mRNA vaccines for HIV are either on the market or being studied.

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In August 2018, the U.S. Food and Treatment Management (FDA) approved Onpattro® (patisiran) (Alnylam Pharmaceuticals Inc., Cambridge, MA, USA) as the first therapeutic use of "RNA interference (siRNA)" following years of research [12]. The carrier system used in the mRNA vaccination technology allows nucleic acids encoding the desired antigen to be delivered into the human host by stimulating the target cell [13]. Thus, the immune response can be triggered for producing the targeted protein and expression of the targeted antigen by the host cell. The system of defense of the host quickly stands immune responses of cellular and humoral in response to the pathogen for the transmission of the antigen, finally putting an end to the disease [14]. Prior to accessing the target cell, mRNA is often encased in a delivery mechanism due to its inherent instability and negative charge. Specifically, when utilizing vaccine delivery systems based on lipid nanoparticles (LNPs), mRNA can only enter cells by endocytosis [15]. By following this process, the integrity of the cell membrane is guaranteed to remain intact while an endosome forms. Inside the cytoplasm, the endosome proceeds to the lysosomes directly for creating destruction. Consequently, it is necessary to avoid the fusion of endosomes with the lysosomes and the disruption subsequently it produces in response to guarantee the stability of structure and, accordingly, transformation of injected mRNA. Escape of endosomes and mRNA release have been demonstrated to be facilitated by ionizable lipids present in LNPs [16].

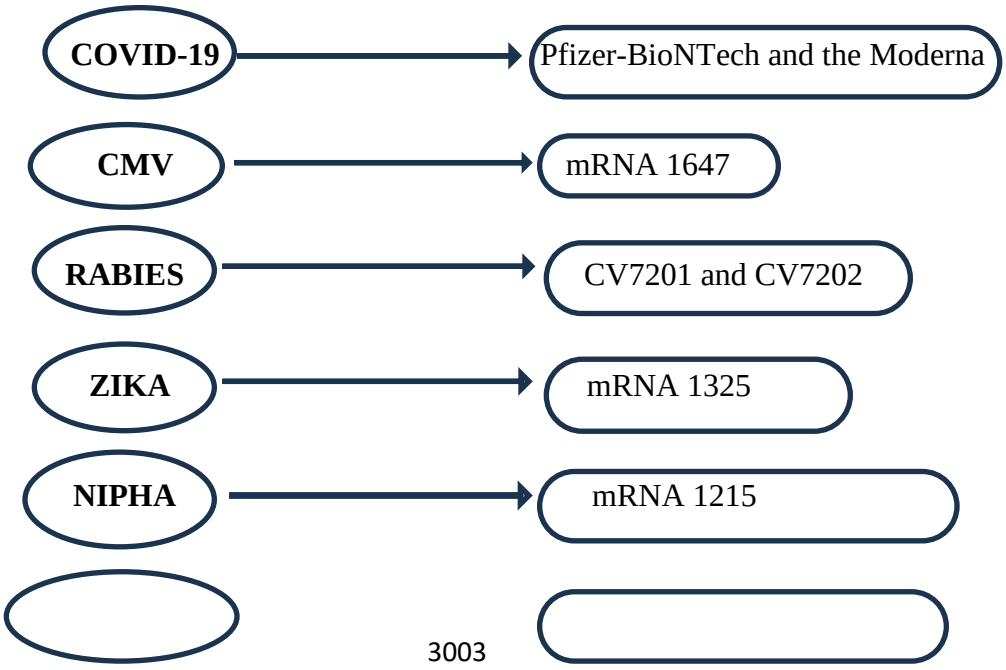

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Figure 2. Numerous mRNA vaccines are available to prevent cancer and infectious disorders.

mRNA vaccine research for the treatment of HIV has produced an encouraging finding. In particular, the study concentrated on an HIV-1 Gag mRNA vaccine that used polyethyleneimine stearic acid (PSA). A capable trial that produced a favourable immunological response was conducted [17].

The National Institutes of Health has introduced the HVTN 302 research, a tiered trial for three mRNA HIV vaccines: i) BG505 MD39.3 mRNA, ii) BG505 MD39.3 gp151 mRNA, and iii) BG505 MD39.3 gp151 CD4KO mRNA [18]. The presence of spike protein that is observed on the surface of HIV to facilitate the entry of the virus into cells of the human body is fused into these available vaccinations [19]. They all encode for different proteins that are connected to each other. The findings showed that nearly all of the recipients of the eOD-GT8 60-mer HIV nanoparticle vaccination generated and enlarged a particular type of B immune cell [20]. To create the version of mRNA, the eOD-GT8 60-mer, the team is presently collaborating with Moderna. During the COVID-19 outbreak, replication-incompetent adenovirus (Ad) vectors and mRNA vaccines were used first widely in the field [21]. Vaccines, in contrast to the viral vector industry, have been evaluated comprehensively. Historically, antibody and cellular responses have been investigated separately. Some disadvantages have been observed in mRNA, even if they are crucial in the fight against the COVID-19 pandemic [22]. These include their disintegration and instability, which make it more difficult to transport, store, and use them in general. For the study of effective administration of vaccines of mRNA, so many proposals for non-viral techniques have been observed. Polyplexes, cationic nano-emulsions (CNEs), and lipid nanoparticles (LNPs) are specifically used in these methods of delivery [23].

Because of the disease's morbidity in immunocompromised and transplant patients, effective cytomegalovirus (CMV) vaccination was necessary. The cytomegalovirus (CMV) is the target of the six mRNAs that comprise the mRNA 1647 vaccine [24]. While the other five encode the complexes of the CMV pentamer, in which one of them encodes the glycoprotein B (gB) protein.

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Interestingly, two highly immunogenic antigens include the complex of the CMV pentamer and the gB protein [25]. This formulation demonstrates the capability of vaccines to provoke a strong immune response, which underscores their potential efficacy. The mRNA 1647 immunization produced larger and more durable antibody responses, according to the results of the most current human trial. Scientific trials for CV7201, the first rabies virus mRNA formulation, began in 2017 [26]. Phase 1 clinical trials concluded that CV7201 and CV7202 demonstrated good effectiveness and immunogenicity.

mRNA vaccines in Zika Virus:

In regards to the human phase 1 scientific trial, Zika virus, Moderna's mRNA vaccines, mRNA-1325 and mRNA-1893, have just concluded. In results, all of these vaccines are found to be well-tolerated by producing a strong immune response [27]. The progression of further clinical research is prompted by these promising outcomes. Developing novel ways of treating cancer, which requires the first clinical research on humans by therapeutic vaccination of cancer by using PSA-transfected dendritic cells [28]. Through clinical trials, more than 20 mRNA-based immunizations have been studied against tumours existing in the human body, like melanoma, lung cancer, and colon-rectal carcinoma [29]. As a result, these trials combine combinations of cytokines or checkpoint modulators (PD-1, CTLA-4, and TIM3) with cancer vaccines of mRNA to promote their effectiveness against the cells of tumours [30].

mRNA vaccines in melanoma:

Notable for being an intravenous vaccine of liposomal RNA (RNA-LPX), the Melanoma FixVac (BNT111) of the mRNA vaccine looks at a new method of melanoma immunotherapy. Targeted are four tumor-associated antigens commonly identified in melanoma that are not changed [31]. This vaccination is currently being tested in patients with advanced melanoma in a phase I study called the trial of the Lipo-MERIT, either single or in combination with inhibitors of checkpoint PD1 inhibition. Responses of patients have been observed to be balanced [32].

Specific mRNA:

A significant turning point for the development of vaccines of mRNA is the generation of tailored vaccinations [33]. For example, the mRNA vaccine of 4157 cancer, which may convert

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up to 34 tumours of neoantigens unique to each patient, showed results in the experiment of KEYNOTE 942. In this study, patients receiving both pembrolizumab and 4157 of mRNA had a nearly 45% decreased risk of death or recurrence compared to those who only received pembrolizumab [34].

In a separate phase 1 clinical trial, autogenous cerumen, a tailored neoantigen vaccine using uridine mRNA lipoplex nanoparticles, showed promise and safety when given with atezolizumab and mFOLFIRINOX [35]. In unselected patients, half in number with operable pancreatic ductal adenocarcinoma, it generated many neoantigen-specific T cells considerably.

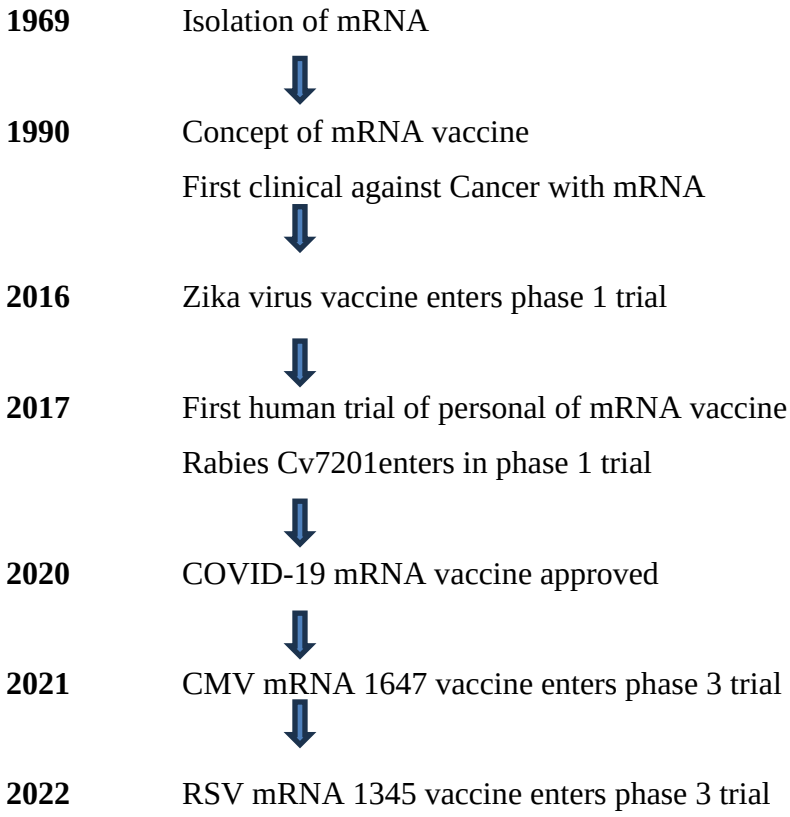

Figure 3. Evolution of mRNA technology timeline for research on vaccines against infectious diseases and malignancies caused by viruses

Optimizing Vectors for Effective mRNA Vaccine Delivery

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After the first generation of mRNA vaccines' shortcomings were addressed, second-generation vaccines were created, maintaining the same level of efficacy and safety but with improved handling, storage, and safety [36]. It will no longer be necessary to use cold chain shipping because the immunizations are found stable at room temperature. The search is extended further for getting more powerful nanocarriers of ligand-targeted efficiency with improved safety and profiles of effective mRNA delivery, which is another concern [37]. In the case of uses of self-amplifying RNA and other RNA-based products, like vaccines, so much research is observed. A standardized thin film of lipid hydration has been seen, which is used to produce a variety of liposomes and LNP [38]. Creating different-sized nanoparticles has shown several disadvantages, one of which is the different heterogeneous particle distribution. In order to obtain LNPs that are homogenous and consistent, the technique of subsequent size-tuning is now needed [39].

Since mRNA is itself a big material with a negative charge, several methods have been developed to get it into cells. These can be generically categorized as vector delivery techniques that are most of the time viral or sometimes non-viral [40]. Systems for delivery based on polymers and lipids are additional categories for non-viral substances. Liposomal complexes and lipo-nanoparticle delivery systems are two types of lipid delivery systems [41].

Recent Advances in mRNA Vaccines

There is a great deal of promise for disease prevention and mitigation around the world thanks to the mRNA vaccine-developed technology. Thanks to recent advances in the area of mRNA vaccines, which is also shown in the viability of this novel immunization strategy, the development of COVID-19 vaccines has moved swiftly [42]. The first COVID-19 vaccine ever approved by the FDA was the product of the COVID-19 pandemic, which acted for mRNA-based vaccine tests ultimately. These vaccines achieved all goals in terms of giving performance [43]. This original and new approach has shown the potential to completely change, and the new way for protein replacement treatment, cancer immunotherapy, vaccination, and other medical practices is carried out today. An incredible tool for combating infectious diseases and potential pandemics is the mRNA vaccination [44]. Owing to their remarkable ability to lower hospitalization and serious illness associated with COVID-19, i) Pfizer (BNT162b2) and ii)

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Moderna (mRNA-1273) vaccines have been licensed for commercial use in the prevention of COVID-19 [45]. The mRNA vaccine's efficacy against novel variations of COVID-19 has also been demonstrated, highlighting the technology's encouraging potential for the prevention of infectious illnesses [46]. The Pfizer-BioNTech vaccine was the first to be approved by the FDA for COVID-19 use in children ages 5 to 11. There are now 17 mRNA vaccines being studied in clinical trials to prevent COVID-19. mRNA vaccine manufacture is a promising method that can quickly and easily respond to new alterations in the genome of the virus, which was developed during the pandemic of COVID-19 [47].

In scientific advancement, these developments are the result of thirty years of approaches. In the past few years, there have also been advancements in the development of mRNA vaccines, which include the efficacy of highly secured, effective mRNA vaccine delivery methods [48]. Innovative manufacturing methods and delivery systems will also enable the rapid and affordable mass production of next-generation mRNA vaccines. Another development in the innovation of different methods for receiving the very quick, simple mRNA mass manufacture in accordance with regulations of cGMP, which can make it possible to produce vaccines of consistently excellent quality. mRNA vaccines are easily degraded and non-infectious, in contrast to regular immunizations [49]. Future use of mRNA vaccines may be made possible by their well-tolerated nature, lack of integration into the host genome, and lack of major health side effects. Additional diseases can be cured, and infectious diseases can be prevented and managed thanks to the mRNA technology platform [50]. The race for the COVID-19 vaccine has influenced the positive impacts and uses of vaccines of mRNA in the replacement of cancer and protein therapies due to their performance.

They can enhance our arsenal of tools for treating cancer and establishing and reemerging communicable diseases by eliciting self-immune responses [51]. mRNA vaccine modulation is designed for the production to handle different application scenarios and has been demonstrated in clinical use [52]. Even though mRNA-based vaccinations have demonstrated encouraging outcomes in terms of safety and effectiveness, more research is required to confirm these outcomes in the whole human population [53]. During the next five years, significant clinical studies for

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vaccines of mRNA, particularly those that are against COVID-19, will come to an end, giving researchers a deeper grip on the mRNA platform vaccines and their variety of methods of delivery [54]. The vaccines of mRNA creation may enhance our ability to combat and control newly emerging infectious diseases. mRNA-based vaccines are a possible replacement for conventional vaccines because they have a number of advantages over traditional vaccinations, including greater efficacy, safety, affordability, and large-scale production [55]. In the future, the latest technology will become capable of inducing change in the course of prevalent infectious diseases by utilizing a safe and dependable way to combat these infectious diseases and cancerous sites [56]. An instruction to produce proteins inside ribosomes by host cells is included in mRNA vaccines, which are designed to produce different immunological responses for activating the body's defenses against infections or malignant cells [57]. With so many possible applications for mRNA vaccine technology, a preferred vaccination pattern might be created. The discovery by Wolff et al. in 1990 that mice could produce a target protein via intramuscular (IM) injection marked the beginning of the history of mRNA [58]. However, because of problems with its unstable nature and distribution, the clinical validation of this innovative technology took several years. Over 190 companies and academic institutions are presently engaged in the development of over 310 mRNA therapies and vaccines. These medications are in a range of development phases, ranging from preclinical research and early discovery to different phases of clinical trials [59]. Vaccines make up the remaining third of these products, with two-thirds (a total of 125) currently in the clinical pipeline worldwide. Most of these products, with the exception of COVID-19 vaccines of mRNA, are notably still in the clinical research of the early phases [60].

In the next step, a further unique approach to treating pancreatic cancer is becoming more widely accessible to patients [61]. A clinical trial in phase II is launched for evaluating the further effectiveness of using the vaccine of mRNA in the fight against disastrous types of cancer based on results from an initial investigation. The purpose of this most current experiment is to find out if the vaccine therapy can reduce the risk of recurrence of pancreatic cancer by following the surgical excision of the tumor [62]. The results of the phase 1 trial show the safe use of mRNA vaccines is safe and may even be able to produce a long-lasting immune response. The study is

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expected to enroll about 260 individuals [63]. Eight of the sixteen patients whose records were reviewed had strong immunological T cell activation as a result of the vaccinations. Compared to individuals who did not respond to the vaccine, those who did exhibit a robust immune response had longer times until cancer reappeared. Based on genomic sequencing, the vaccine of mRNA-4157 can encode up to specific neoantigens of 34 patients, which can be generated in around six weeks [64].

The companies plan to look into how well the treatment works for non-small-cell lung cancer. This accomplishment shows how mRNA vaccines can target a wide range of neoantigens, and it also stands in contrast to previous barriers in the creation of anti-cancer vaccinations [65]. Although the exact reason for the variation in melanoma's response to immunotherapy remains unknown, it may be related to the quality other than neoantigen quantity [66]. In spite of failures of previous experiments, the vaccine of the mRNA technique has generated since it leverages the effectiveness of immunotherapy and tailored targeting for specific cancers [67]. Clinical trials using modified primary human T cells in the form of CRISPR are currently being carried out for the treatment of metastatic gastrointestinal cancer. This advanced medication aims to target cytokine-inducible SH2-containing protein (CISH), an intracellular gatekeeper that was previously believed to be undruggable. Most importantly, it has the specific design to maintain the function and viability of cells [68].

Aiming for the vaccination, which must be proper, safe, and effective against the Zika virus, individuals of healthy age (18 to 49) took part in randomized, placebo-controlled attempts to assess the protection, immunity, and neutralizing antibodies (nAbs) specific to the virus [69]. Examined in the USA, mRNA-1325 exhibited mild nAb responses but showed general tolerability at dose levels of 10, 25, and 100 µg. By day 57, all of the subjects in the United States and Puerto Rico who received the mRNA-1893 vaccine developed robust and durable antibody responses specific to the Zika virus, regardless of their flavivirus serostatus. Nevertheless, at greater doses, the majority of the negative effects were mild to moderate. These positive results highlight the safety and effectiveness of mRNA-1893 in generating strong anti-Zika antibody responses, hence supporting its development [70].

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Additionally, researchers working on mRNA vaccines have the Nipah virus in their sights. Although humans can contract this zoonotic virus and suffer life-threatening repercussions, such as coma or even death, it primarily spreads through animals [71]. The National Institutes of Health (NIH) initiated a trial at an early stage to evaluate a vaccine for an experiment with a defensive motivation, as there is currently no approved treatment or vaccine available for the treatment of Nipah virus infection [72]. The efficacy of mRNA vaccines against various cancers and infectious illnesses is being studied through extensive clinical trials. Furthermore, a clinical experiment aimed at treating sickle cell disease with the adenine base editor (ABE) has been going on (Table 1).

Table 1. List of ongoing clinical trials evaluating the role of mRNA vaccines in cancer.

ID for Clinical Trait	**Type of Study**	**Phase**	**Population**	**Groups**	**Primary Outcomes**
NCT05968326	Multicellular, Randomized	II	Patients (n = 260) with resected pancreatic ductal adenocarcinoma	1. Autogene cevumeran (mRNA) + atezolizumab + folfirinox 2. Folfirinox alone	Disease-free survival
NCT03897881	Randomized	III	Patients after complete resection of high-risk melanoma	1. mRNA-4157 + pembrolizumab 2. Pembrolizumab alone	Recurrence-free survival (RFS), assessed using radiological imaging

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NCT05198752	Open Label	I	Patients with advanced malignant solid tumors	SW1115C3 (mRNA)	Dose-limiting toxicity incidence
NCT04382898	Multicellular, Randomized Four-arm	I/II	Patients with high-risk, localized prostate cancer	1. BNT112 2. BNT112 + cemiplimab	Dose-limiting toxicity, adverse events, objective response rate
NCT05192460	Single center, single-arm	Not applicable	Patients with advanced gastric cancer, esophageal cancer, and liver cancer	1. mRNA + PD-1/L1 2. mRNA alone	Adverse events, objective response rate

Improving the stability of mRNA vaccines for infectious diseases and virus-induced cancers

The field of vaccination has seen a complete transformation thanks to mRNA vaccines, which offer a rapid and flexible way for fighting diseases of different infections and cancers that are induced virally [73]. But its intrinsic volatility poses a significant barrier to their broader adoption. In the last few years, scientists have concentrated on increasing the chances of improving mRNA vaccine stability in order to enhance the efficacy, storage, and release of these vaccines [74]. Durability is a crucial factor in the efficacy and broad application of mRNA vaccines. The primary objective of ongoing research efforts has been to find solutions for the problems caused by mRNA instability. It has been discovered that several methods for enhancing the mRNA

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vaccines maturity offer positive expectations for their widespread use in the management of virally induced cancers and infectious disorders [75]. Improving mRNA distribution with lipid nanoparticle (LNP) formulations is one such tactic. LNPs can protect and stabilize mRNA molecules. The development of LNPs by Zhang et al. was centered on optimizing mRNA packaging, stability, and cellular uptake to raise the impact of vaccination [76]. A similar investigation investigating the effective administration of mRNA vaccines using stable lipid formulations was conducted by Allen and Mout. RNA can also be stabilized by modified nucleosides [77].

In order to increase vaccine durability, Feng et al. (2023) concentrated on the logical design of modified nucleosides, which can improve mRNA stability and shield the mRNA molecule from degradation[78]. To achieve even more stability, mRNA sequence and alteration optimization are essential. Li and Wang (2022) have identified two techniques that can enhance mRNA stability and translation efficiency, ultimately leading to more efficient protein synthesis: codon optimization and the incorporation of modified nucleotides. Stability of temperature for mRNA vaccines is a significant problem, particularly in storage and transit. In order to improve mRNA vaccines' thermostability, Chen and Kim (2022) discussed how to alter the RNA structures and incorporate stabilizing chemicals. These strategies aimed to preserve vaccine efficacy and extend shelf life by preventing the mRNA molecule from breaking down at different temperatures. To address doubts about the mRNA vaccine’s stability, the development and formulation of different strategies are being observed. Riedmann and Cooney (2022) brought several techniques and methodologies for formulation, like bringing stable excipients and coats for protection, for overcoming the instability for treatments of inherent RNA. Preserving mRNA integrity during distribution and storage was the aim of these strategies. Lallana and Rincón-López (2022) carried out an exhaustive investigation of different concerns about its stability and delivery, which are linked directly with vaccines of mRNA. They also bring focus to different methods of solutions for the resolution of these issues by explaining the strategies working to enhance stability and the challenges related to implementation.

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Since mRNA vaccines are still being stabilized, there are generally promising prospects to improve their efficacy and utility. Enhancing LNP formulations, logically creating changed nucleosides, refining mRNA sequences, and creating formulation methods are all helping researchers build the foundation for more stable vaccines of mRNA [79]. These mature types of advancements further enable the widespread application of vaccines of mRNA in the fight between viral malignant and some other infectious diseases while also making mRNA vaccines easier to store and provide.

Formulation and Delivery of mRNA Vaccines

Following are the stages involved in creating and administering mRNA vaccines:

a. Injection of naked mRNA:

It is possible to provide naked mRNA immediately following reconstitution using an appropriate buffer, like Ringer's solution or its lactate. There are several ways to give the medication locally, including intramuscular, intranodal, and intranasal methods, in order to shorten the duration that the vaccine is exposed to RNases in the bloodstream. Still, their capacity to cross the lipid bilayer is restricted, and they are susceptible to RNases [80].

Uncovered mRNAs are currently observed in different clinical trials that are carried out for the treatment of melanoma and hepatocellular carcinoma (Figure 3).

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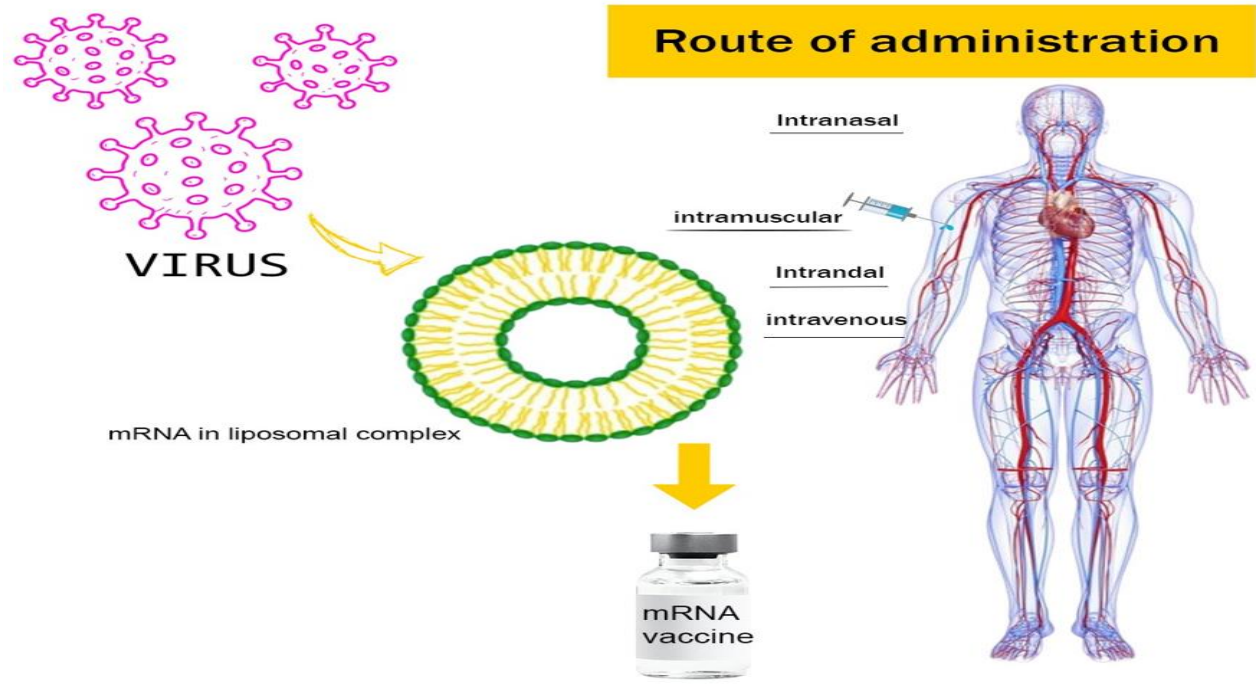

Figure 3: Liposomal complex vaccine development and common routes of administration of mRNA vaccines.

b. Liposomal complexes:

Phospholipid layers, which comprise liposomes, are positively charged cationic lipids that include an mRNA vaccination core that keeps RNase from accessing them. These liposomal complexes are easily degradable due to their positive charge, even in healthy conditions [81].

c. Lipid nanoparticles:

LNPs are composed of an mRNA vaccine that holds an aqueous covering along with cholesterol, glycol of polyethene, auxiliary lipids, and shells of the lipid bilayer. LNPs, in contrast to liposomal complexes, are made up of a range of distinct lipids that support their structural stability [82].

d. Modification of LNPs:

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The short blood circulation period, instability in vivo, and selection of a lack of target LNPs can all be moderated by bringing any modification. This alteration includes targeted liposomes with ligands that are surface-bound. Through the use of the ligands unique to each receptor, liposomes have been employed, for instance, to target the overexpressed folate and transferrin receptors in cancer cells [83]. Thanks to their high binding affinity for folic acid, folate receptors have the ability to specifically target tumor cells. However, in malignancies like cancers of the lung, colorectal, and breast, EGFR is overexpressed on a large number of cells. In other words, drugs can be delivered to harmful cells by targeting EGFR [84].

e. Stimulus-responsive liposomes:

Modified stimulus-responsive liposomes contain medications that are released in response to bringing a few changes, like modifications in temperature, pH, light, enzymes, some electrical and magnetic fields, ultrasound, and other stimuli [85]. A pH shift is the most promising trigger because the body is full of pH gradients. Upon activation, some types of liposomes undergo a period of change that helps in the enhancement of the permeability of the membrane and allows for the drug to be released in a burst [86].

f. delivery systems, i.e., polymer-based:

These delivery methods of mRNA are special because they can be detected and form nanostructures in aqueous environments and contain some special type of pharmacokinetics. Nevertheless, concerns exist regarding its effectiveness and toxin probability in their limited type of transfection [87]. They require tremendous reproducibility, chemical structural control, and explicit polymer engineering to be turned into therapeutics. An example of an extra nanoparticle substance is ferritin. It has been shown that the ferro nanoparticle vaccine completely eradicates the mice having the hepatitis B virus by undergoing numerous clinical studies that are currently in progress [88].

Since mRNAs are so large, intrinsically unstable, charged, and more prone to enzyme breakdown in the lab during clinical settings, numerous challenges are also observed during mRNA-based delivery approaches [89]. Future applications of vaccines of mRNA are found difficult since the accessory standards of the mRNA can be altered by the delivery system as well.

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This means that the need for better drug delivery systems is required to bring delay in the broader arrangement of therapies, which must be mRNA-based [90]. It is found that vaccines are extremely temperature sensitive; in concern of their manufacture, composition, storage, and delivery, they need to be kept within a temperature-specific range to maintain their long-term effectiveness. However, some chains of mRNA vaccines possibly need even lower temperatures than their requirements for preserving and distributing these vaccines. Some vaccines of mRNA are still challenged by the cold storage requirement [91]. The maintenance of vaccines of mRNA at a particular temperature is required in case of instability of the LNP mRNA system. This instability, low efficacy translation, and targeting of poor cells of naked mRNA can be controlled by different sophisticated methods of delivery techniques [92]. Still, it appears that mRNA vaccine delivery technologies need to be refined, given that a large number of clinically evaluated mRNA vaccine candidates lacked a conveyance mechanism.

Conclusion:

In the practical age of scientific inquiry, vaccines of mRNA have brought a highly promising platform for the development of vaccines. The disastrous pandemic of COVID-19 has allowed some advancements in the formation of mRNA vaccines for the treatment and prevention of several other infectious diseases. This has led to a gradual increase in the availability and public awareness of a new generation of immunizations. When replying to the latest developments in the field of viral genomes, mRNA vaccines can be utilized to change the structure of the antigen and even merge unique sequences from other versions. Present-day mRNA immunizations provide enough safety and protection; nevertheless, more clinical study is required to find out how long the protection lasts. Thus, more investigation and development into the stability of mRNA vaccines are needed.

REFERENCES

[1] D. Bafaloukos, I. Gazouli, C. Koutserimpas, and G. Simonis, “Evolution and Progress of mRNA Vaccines in the Treatment of Melanoma: Future Prospects,” *Vaccines*, vol. 11, no. 3, 2023, doi: 10.3390/vaccines11030636.

[2] S. Qin *et al.*, “mRNA-based therapeutics: powerful and versatile tools to combat diseases,”

Signal Transduction and Targeted Therapy, vol. 7, no. 1. 2022. doi: 10.1038/s41392-022-01007-w.

[3] Y. Mei and X. Wang, "RNA modification in mRNA cancer vaccines," *Clinical and Experimental Medicine*, vol. 23, no. 6. 2023. doi: 10.1007/s10238-023-01020-5.

[4] J. K. Hwang, T. Zhang, A. Z. Wang, and Z. Li, "COVID-19 vaccines for patients with cancer: benefits likely outweigh risks," *Journal of Hematology and Oncology*, vol. 14, no. 1. 2021. doi: 10.1186/s13045-021-01046-w.

[5] W. Yihunie, G. Nibret, and Y. Aschale, "Recent Advances in Messenger Ribonucleic Acid (mRNA) Vaccines and Their Delivery Systems: A Review," *Clinical Pharmacology: Advances and Applications*, vol. 15. 2023. doi: 10.2147/CPAA.S418314.

[6] I. Berdeu, D. Spătaru, and A. Paraschiv, "VACCINES: PAST, PRESENT AND FUTURE," *One Heal. Risk Manag.*, vol. 2, no. 2, 2021, doi: 10.38045/ohrm.2021.2.04.

[7] A. Y. Shchaslyvyi, S. V. Antonenko, M. G. Tesliuk, and G. D. Telegeev, "Current State of Human Gene Therapy: Approved Products and Vectors," *Pharmaceuticals*, vol. 16, no. 10. 2023. doi: 10.3390/ph16101416.

[8] X. Chen *et al.*, "NAT10/ac4C/FOXP1 Promotes Malignant Progression and Facilitates Immunosuppression by Reprogramming Glycolytic Metabolism in Cervical Cancer," *Adv. Sci.*, vol. 10, no. 32, 2023, doi: 10.1002/advs.202302705.

[9] M. Diken, L. M. Kranz, S. Kreiter, and U. Sahin, "mRNA: A Versatile Molecule for Cancer Vaccines," *Current issues in molecular biology*, vol. 22. 2017. doi: 10.21775/cimb.022.113.

[10] R. C. Steffens and E. Wagner, "Directing the Way—Receptor and Chemical Targeting Strategies for Nucleic Acid Delivery," *Pharmaceutical Research*. 2022. doi: 10.1007/s11095-022-03385-w.

[11] L. Ma, Z. Liang, H. Zhou, and L. Qu, "Applications of RNA Indexes for Precision Oncology in Breast Cancer," *Genomics, Proteomics and Bioinformatics*, vol. 16, no. 2. 2018. doi: 10.1016/j.gpb.2018.03.002.

[12] D. Pozzi and G. Caracciolo, "Looking Back, Moving Forward: Lipid Nanoparticles as a Promising Frontier in Gene Delivery," *ACS Pharmacology and Translational Science*, vol. 6, no. 11. 2023. doi: 10.1021/acsptsci.3c00185.

[13] P. Joshi, K. Kalra, and D. Ghalwan, "A detail study of corona vaccine effect on cancer patients," *Onkol. i Radioter.*, vol. 16, no. 3, 2022.

[14] S. Pellegrino, S. Terrosu, G. Yusupova, and M. Yusupov, "Inhibition of the eukaryotic 80S ribosome as a potential anticancer therapy: A structural perspective," *Cancers*, vol. 13, no. 17. 2021. doi: 10.3390/cancers13174392.

[15] Z. Qin, L. Qin, X. Feng, Z. Li, and J. Bian, "Development of Cdc2-like Kinase 2 Inhibitors: Achievements and Future Directions," *Journal of Medicinal Chemistry*, vol. 64, no. 18. 2021. doi: 10.1021/acs.jmedchem.1c00985.

[16] M. S. Singh and D. Peer, "RNA nanomedicines: The next generation drugs?," *Current Opinion in Biotechnology*, vol. 39. 2016. doi: 10.1016/j.copbio.2015.12.011.

[17] P. Ji, X. Wang, N. Xie, and Y. Li, "N6-methyladenosine in RNA and DNA: An epitranscriptomic and epigenetic player implicated in determination of stem cell fate," *Stem Cells International*, vol. 2018. 2018. doi: 10.1155/2018/3256524.

[18] N. P. Long *et al.*, "Systematic assessment of cervical cancer initiation and progression uncovers genetic panels for deep learning-based early diagnosis and proposes novel diagnostic and prognostic biomarkers," *Oncotarget*, vol. 8, no. 65, 2017, doi: 10.18632/oncotarget.22689.

[19] M. A. Stoff-Khalili *et al.*, "Cancer-specific targeting of a conditionally replicative adenovirus using mRNA translational control," *Breast Cancer Res. Treat.*, vol. 108, no. 1, 2008, doi: 10.1007/s10549-007-9587-7.

[20] K. J. Paddock, K. S. Veum, D. L. Finke, A. C. Ericsson, and B. E. Hibbard, "Correction: Soil microbes from conservation agriculture systems reduce growth of Bt-resistant western corn rootworm larvae," *J. Pest Sci. (2004).*, vol. 97, no. 3, 2024, doi: 10.1007/s10340-024-01751-8.

[21] M. Rai *et al.*, "Copper and copper nanoparticles: Role in management of insect-pests and pathogenic microbes," *Nanotechnology Reviews*, vol. 7, no. 4. 2018. doi: 10.1515/ntrev-2018-0031.

[22] W. Jin *et al.*, "Continuous remote sensing ecological index (CRSEI): A novel approach for multitemporal monitoring of eco-environmental changes on large scale," *Ecol. Indic.*, vol. 154, 2023, doi: 10.1016/j.ecolind.2023.110739.

[23] X. Huang and Z. Jia, "Construction of HCC-targeting artificial miRNAs using natural miRNA precursors," *Exp. Ther. Med.*, vol. 6, no. 1, 2013, doi: 10.3892/etm.2013.1111.

[24] J. Danneck *et al.*, "Conserving urban tropical biodiversity by connecting networks of green patches," *Integr. Conserv.*, vol. 2, no. 2, 2023, doi: 10.1002/inc3.21.

[25] G. Esposito, "Complementary techniques: Laser capture microdissection - Increasing specificity of gene expression profiling of cancer specimens," *Advances in Experimental Medicine and Biology*, vol. 593. 2007. doi: 10.1007/978-0-387-39978-2_6.

[26] Y. Raj, A. Kumar, S. Kumari, R. Kumar, and R. Kumar, "Comparative Genomics and Physiological Investigations Supported Multifaceted Plant Growth-Promoting Activities in Two Hypericum perforatum L.-Associated Plant Growth-Promoting Rhizobacteria for Microbe-Assisted Cultivation," *Microbiol. Spectr.*, vol. 11, no. 3, 2023, doi: 10.1128/spectrum.00607-23.

[27] C. 2022, "cochrane 2022," *J. Am. Acad. Dermatol.*, vol. 10, no. 1, 2018.

[28] J. Huang *et al.*, "C-Myc modulates glucose metabolism via regulation of miR184/PKM2 pathway in clear-cell renal cell carcinoma," *Int. J. Oncol.*, vol. 49, no. 4, 2016, doi: 10.3892/ijo.2016.3622.

[29] S.-E. Lee, J. Y. Lee, A.-R. Han, W.-S. Min, and H. Kim, "Clinical Impact of Different Levels of VEGF-C on Leukemic Blasts in the Bone Marrow and Peripheral Blood of Acute Myeloid Leukemia," *Blood*, vol. 128, no. 22, 2016, doi: 10.1182/blood.v128.22.1670.1670.

[30] V. F. Semiglazov *et al.*, "Clinical and biological model for evaluation of the effectiveness of systemic therapy for breast cancer," *Vopr. Onkol.*, vol. 64, no. 3, 2018, doi: 10.37469/0507-3758-2018-64-3-289-297.

[31] N. Ehsan, G. Hoogenboom, M. K. Qamar, C. J. Wilkerson, S. A. Wajid, and F. Aziz, "Climate change risk perception and adaptation to climate smart agriculture are required to increase wheat production for food security," *Ital. J. Agron.*, vol. 17, no. 4, 2022, doi: 10.4081/ija.2022.2129.

[32] M. Zachariah *et al.*, "Climate Change made devastating early heat in India and Pakistan 30 times more likely," *World Weather Attrib.*, vol. 56, no. 2, 2022.

[33] J. Dong *et al.*, "Circulating tumor cells in pulmonary vein and peripheral arterial provide a metric for PD-L1 diagnosis and prognosis of patients with non-small cell lung cancer," *PLoS One*, vol.

14, no. 7, 2019, doi: 10.1371/journal.pone.0220306.

[34] A. Gutkin *et al.*, "Circulating hTERT (human telomerase) mRNA: mechanism of action and potential use for early diagnosis of malignancy," *J. Extracell. Vesicles*, vol. 4, 2015.

[35] J. Chen *et al.*, "Circular RNA circRHOBTB3 represses metastasis by regulating the HuR-mediated mRNA stability of PTBP1 in colorectal cancer," *Theranostics*, vol. 11, no. 15, 2021, doi: 10.7150/THNO.56990.

[36] G. Li *et al.*, "CircRNA hsa_circ_0014130 function as a miR-132-3p sponge for playing oncogenic roles in bladder cancer via upregulating KCNJ12 expression," *Cell Biol. Toxicol.*, vol. 38, no. 6, 2022, doi: 10.1007/s10565-021-09668-z.

[37] Y. Wang *et al.*, "Circ_0007031 serves as a sponge of MiR-760 to regulate the growth and chemoradiotherapy resistance of colorectal cancer via regulating dcp1a," *Cancer Manag. Res.*, vol. 12, 2020, doi: 10.2147/CMAR.S254815.

[38] W. Shao *et al.*, "Characterizing the Survival-Associated Interactions Between Tumor-Infiltrating Lymphocytes and Tumors From Pathological Images and Multi-Omics Data," *IEEE Trans. Med. Imaging*, vol. 42, no. 10, 2023, doi: 10.1109/TMI.2023.3274652.

[39] S. H. Heo *et al.*, "Characterization of circulating IL-7R positive cell populations for early detection of pancreatic ductal adenocarcinoma," *J. Clin. Med.*, vol. 10, no. 18, 2021, doi: 10.3390/jcm10184157.

[40] D. S. Metselaar *et al.*, "Celastrol-induced degradation of FANCD2 sensitizes pediatric high-grade gliomas to the DNA-crosslinking agent carboplatin," *EBioMedicine*, vol. 50, 2019, doi: 10.1016/j.ebiom.2019.10.062.

[41] A. Giuliani, "Cancer mRNA Vaccines as a Promising Approach for Treating Luminal A Breast Cancer," *Int. J. High Sch. Res.*, vol. 4, no. 3, 2022, doi: 10.36838/v4i3.5.

[42] R. J. Van Barneveld *et al.*, "Bone Health in Gynecologic Cancers-does FOSAVANCE Help?," *Am. J. Clin. Nutr.*, vol. 10, no. 1, 2019.

[43] P. E. Saw, X. Xu, S. Kim, and S. Jon, "Biomedical Applications of a Novel Class of High-Affinity Peptides," *Acc. Chem. Res.*, vol. 54, no. 18, 2021, doi: 10.1021/acs.accounts.1c00239.

[44] H. Yan *et al.*, "Association of a cytarabine chemosensitivity related gene expression signature

with survival in cytogenetically normal acute myeloid leukemia," *Oncotarget*, vol. 8, no. 1, 2017, doi: 10.18632/oncotarget.13650.

[45] J. M. Eastel *et al.*, "Application of NanoString technologies in companion diagnostic development," *Expert Review of Molecular Diagnostics*, vol. 19, no. 7. 2019. doi: 10.1080/14737159.2019.1623672.

[46] A. Tellería-Díaz, "Antisense targeting in neurology," *Rev. Neurol.*, vol. 31, no. 8, 2000, doi: 10.33588/rn.3108.2000326.

[47] J. Prins, E. G. E. de Vries, and N. H. Mulder, "Antisense of oligonucleotides and the inhibition of oncogene expression," *Clinical Oncology*, vol. 5, no. 4. 1993. doi: 10.1016/S0936-6555(05)80238-9.

[48] H. Sasano, T. Suzuki, and T. Moriya, "Analysis of surrogate markers for target-specific therapy in breast carcinomas using archival materials," *Biomed. Pharmacother.*, vol. 61, no. 9 SPEC. ISS., 2007, doi: 10.1016/j.biopha.2007.08.019.

[49] A. Gatsiou, N. Vlachogiannis, F. F. Lunella, M. Sachse, and K. Stellos, "Adenosine-to-Inosine RNA Editing in Health and Disease," *Antioxidants and Redox Signaling*, vol. 29, no. 9. 2018. doi: 10.1089/ars.2017.7295.

[50] F. Marme *et al.*, "Abstract P3-06-08: Ki-67 mRNA as a predictor for response to neoadjuvant chemotherapy in primary breast cancer," *Cancer Res.*, vol. 72, no. 24_Supplement, 2012, doi: 10.1158/0008-5472.sabcs12-p3-06-08.

[51] S. Saracchini *et al.*, "Abstract P1-10-23: Prediction of pathological complete response (pCR) upon neoadjuvant chemotherapy by MammaTyper® pCR score," *Cancer Res.*, vol. 80, no. 4_Supplement, 2020, doi: 10.1158/1538-7445.sabcs19-p1-10-23.

[52] C. Pan *et al.*, "Abstract LB-32: Patient-derived xenograft (PDX) paraclinical platform to guide precision medicine in urothelial cancer," *Cancer Res.*, vol. 74, no. 19_Supplement, 2014, doi: 10.1158/1538-7445.am2014-lb-32.

[53] A. Martin-Vega, S. Eartnest, J. D. Minna, J. E. Johnson, and M. H. Cobb, "Abstract LB030: Mechanisms of ERK action in MEK inhibitor-insensitive lung cancers," *Cancer Res.*, vol. 82, no. 12_Supplement, 2022, doi: 10.1158/1538-7445.am2022-lb030.

[54] Y. Kamioka and M. Matsuda, "Abstract B58: Visualization of ERK and PKA activities in the tumor microenvironment comprising of lung-metastasized 4T1 murine breast tumor cells," *Cancer Res.*, vol. 75, no. 1_Supplement, 2015, doi: 10.1158/1538-7445.chtme14-b58.

[55] H. Kim *et al.*, "Abstract B130: The intratumoral heterogeneity of glioblastoma suggests a pivotal role for clonal evolution.," *Mol. Cancer Ther.*, vol. 12, no. 11_Supplement, 2013, doi: 10.1158/1535-7163.targ-13-b130.

[56] R. Nicolle *et al.*, "Abstract A48: Multi-omics characterization of PDAC subtypes using PDX reveals that epigenetic but not genetic analysis permit a clinically relevant classification," *Cancer Res.*, vol. 76, no. 24_Supplement, 2016, doi: 10.1158/1538-7445.panca16-a48.

[57] M. M. A. Valenzuela, I. V. Castro, J. R. Aspe, J. Neidigh, and N. R. Wall, "Abstract A22: Exosomal release of IAPs may contribute to chemoresistance and aggressiveness in pancreatic cancer.," 2012. doi: 10.1158/1538-7445.panca2012-a22.

[58] S. Saxena *et al.*, "Abstract 6194: Evaluation of the differential expression profile of CXC-receptor-2 ligands for potential biomarker candidates in pancreatic ductal adenocarcinoma," *Cancer Res.*, vol. 80, no. 16_Supplement, 2020, doi: 10.1158/1538-7445.am2020-6194.

[59] O. Uziel *et al.*, "Abstract 5219: Circulating hTERT (human telomerase) mRNA: mechanism of action and potential use for early diagnosis of malignancy," *Cancer Res.*, vol. 75, no. 15_Supplement, 2015, doi: 10.1158/1538-7445.am2015-5219.

[60] W. Jang *et al.*, "Abstract 4279: The genomic profile investigation of metastatic triple-negative breast cancer for precision medicine achievement," *Cancer Res.*, vol. 78, no. 13_Supplement, 2018, doi: 10.1158/1538-7445.am2018-4279.

[61] R. Liang *et al.*, "Abstract 4012: Preclinical development of SHP2 allosteric inhibitor ICP-189," *Cancer Res.*, vol. 83, no. 7_Supplement, 2023, doi: 10.1158/1538-7445.am2023-4012.

[62] L. Chee *et al.*, "Abstract 1548: Genetic biomarkers predict clinical response and survival in myelodysplasia," *Cancer Res.*, vol. 78, no. 13_Supplement, 2018, doi: 10.1158/1538-7445.am2018-1548.

[63] D. K. Smith, N. Venugopal, M. K. Terris, and B. L. Lokeshwar, "Abstract 123A: The critical role of interleukin-8 chemokine axis in the development of benign prostatic hyperplasia (BPH),"

Cancer Res., vol. 79, no. 13_Supplement, 2019, doi: 10.1158/1538-7445.am2019-123a.

[64] Y. Ma *et al.*, "Organic fertilizer substitution over six years improves the productivity of garlic, bacterial diversity, and microbial communities network complexity," *Appl. Soil Ecol.*, vol. 182, 2023, doi: 10.1016/j.apsoil.2022.104718.

[65] M. M. Obaid Al-Jumaili, "A Potential Interpretation of RNA Interference and GC Island Modification in Progressive Colorectal Cancer Suppression," *Biomed. Biotechnol. Res. J.*, vol. 7, no. 3, 2023, doi: 10.4103/bbrj.bbrj_145_23.

[66] L. Chen, P. F. Koh, H. K. Lim, and A. P. Kumar, "1047 POSTER Annexin-A1 Mediates Chemosensitivity to PPAR-gamma Ligands in Mammary Carcinoma: a Novel Biomarker for Effective Tailoring of Patients to PPAR-gamma Ligand Therapy," *Eur. J. Cancer*, vol. 47, 2011, doi: 10.1016/s0959-8049(11)70690-6.

[67] X. Huang *et al.*, " Abstract 1111: Synthetic microRNA (miR)-181a nanoparticles (NP) target RAS and sensitize cells to daunorubicin (DNR) in acute myeloid leukemia (AML) ," *Cancer Res.*, vol. 72, no. 8_Supplement, 2012, doi: 10.1158/1538-7445.am2012-1111.

[68] IRCT20180714040462N1 *et al.*, "Effect of blue light from electronic devices on melatonin and sleep/wake rhythmsn high school children," *Sleep*, vol. 40, no. 1, 2020.

[69] D. Weissman, "mRNA transcript therapy," *Expert Review of Vaccines*, vol. 14, no. 2. 2014. doi: 10.1586/14760584.2015.973859.

[70] M. El-Tanani *et al.*, "Impact of exosome therapy on pancreatic cancer and its progression," *Medical Oncology*, vol. 40, no. 8. 2023. doi: 10.1007/s12032-023-02101-x.

[71] P. Lei, J. Zhang, P. Liao, C. Ren, J. Wang, and Y. Wang, "Current progress and novel strategies that target CDK12 for drug discovery," *European Journal of Medicinal Chemistry*, vol. 240. 2022. doi: 10.1016/j.ejmech.2022.114603.

[72] E. Yilmaz, "New hopes in vaccine technology: MRNA vaccines," *Mikrobiyoloji Bulteni*, vol. 55, no. 2. 2021. doi: 10.5578/mb.20219912.

[73] J. J. G. Marin *et al.*, "Impact of alternative splicing variants on liver cancer biology," *Cancers*, vol. 14, no. 1. 2022. doi: 10.3390/cancers14010018.

[74] D. Jain, S. K. Prajapati, A. Jain, and R. Singhal, "Nano-formulated siRNA-based therapeutic

approaches for cancer therapy," *Nano Trends*, vol. 1, 2023, doi: 10.1016/j.nwnano.2023.100006.

[75] Y. H. Taguchi, "Identification of more feasible microRNA-mRNA interactions within multiple cancers using principal component analysis based unsupervised feature extraction," *Int. J. Mol. Sci.*, vol. 17, no. 5, 2016, doi: 10.3390/ijms17050696.

[76] Y. Zhang *et al.*, "METTL3-mediated N6-methyladenosine modification and HDAC5/YY1 promote IFFO1 downregulation in tumor development and chemo-resistance," *Cancer Lett.*, vol. 553, 2023, doi: 10.1016/j.canlet.2022.215971.

[77] O. B. Garbuzenko, M. Saad, V. P. Pozharov, K. R. Reuhl, G. Mainelis, and T. Minko, "Inhibition of lung tumor growth by complex pulmonary delivery of drugs with oligonucleotides as suppressors of cellular resistance," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 107, no. 23, 2010, doi: 10.1073/pnas.1004604107.

[78] I. Patro, A. Sahoo, B. R. Nayak, R. Das, S. Majumder, and G. K. Panigrahi, "Nonsense-Mediated mRNA Decay: Mechanistic Insights and Physiological Significance," *Molecular Biotechnology*. 2023. doi: 10.1007/s12033-023-00927-4.

[79] T. Sibbritt, H. R. Patel, and T. Preiss, "Mapping and significance of the mRNA methylome," *Wiley Interdiscip. Rev. RNA*, vol. 4, no. 4, 2013, doi: 10.1002/wrna.1166.

[80] K. Voglova, J. Bezakova, and I. Herichova, "Micro RNAs: An arguable appraisal in medicine," *Endocr. Regul.*, vol. 50, no. 2, 2016, doi: 10.1515/enr-2016-0013.

[81] L. Scarabel *et al.*, "Strategies to optimize siRNA delivery to hepatocellular carcinoma cells," *Expert Opinion on Drug Delivery*, vol. 14, no. 6. 2017. doi: 10.1080/17425247.2017.1292247.

[82] Y. Yao, S. C. Mack, and M. D. Taylor, "Molecular genetics of ependymoma," *Chinese Journal of Cancer*, vol. 30, no. 10. 2011. doi: 10.5732/cjc.011.10129.

[83] F. C. Jiang *et al.*, "Downregulation of zinc finger protein 71 in laryngeal squamous cell carcinoma tissues and its potential molecular mechanism and clinical significance: a study based on immunohistochemistry staining and data mining," *World J. Surg. Oncol.*, vol. 20, no. 1, 2022, doi: 10.1186/s12957-022-02823-8.

[84] Q. D. Zhang, Z. X. Chen, F. Y. Li, and Y. Zhang, "Research Progress of siRNA Nano-delivery System," *Prog. Biochem. Biophys.*, vol. 49, no. 6, 2022, doi: 10.16476/j.pibb.2021.0102.

[85] J. Li, Y. Xiao, H. Yu, X. Jin, S. Fan, and W. Liu, "Mutual connected IL-6, EGFR and LIN28/Let7-related mechanisms modulate PD-L1 and IGF upregulation in HNSCC using immunotherapy," *Frontiers in Oncology*, vol. 13. 2023. doi: 10.3389/fonc.2023.1140133.

[86] Z. Wu *et al.*, "Significance of S100P as a biomarker in diagnosis, prognosis and therapy of opisthorchiasis-associated cholangiocarcinoma," *Int. J. Cancer*, vol. 138, no. 2, 2016, doi: 10.1002/ijc.29721.

[87] L. J. Song *et al.*, "PU.1 is identified as a novel metastasis suppressor in hepatocellular carcinoma regulating the miR-615-5p/IGF2 axis," *Asian Pacific J. Cancer Prev.*, vol. 16, no. 9, 2015, doi: 10.7314/APJCP.2015.16.9.3667.

[88] M. L. Eide and H. Debaque, "Méthodes de détection des HPVs et techniques de génotypage dans le dépistage du cancer du col utérin," *Annales de Pathologie*, vol. 32, no. 6. 2012. doi: 10.1016/j.annpat.2012.09.200.

[89] V. Sian, J. A. Souto, R. Alvarez, A. Nebbioso, A. R. de Lera, and L. Altucci, "Inhibitors of Jumonji-C domain-containing histone demethylases," in *Epigenetic Cancer Therapy, Second Edition*, 2023. doi: 10.1016/B978-0-323-91367-6.00025-8.

[90] C. Hartshorn, J. J. Eckert, O. Hartung, and L. J. Wangh, "Single-cell duplex RT-LATE-PCR reveals Oct4 and Xist RNA gradients in 8-cell embryos," *BMC Biotechnol.*, vol. 7, 2007, doi: 10.1186/1472-6750-7-87.

[91] L. Li, S. Hu, and X. Chen, "Non-viral delivery systems for CRISPR/Cas9-based genome editing: Challenges and opportunities," *Biomaterials*, vol. 171. 2018. doi: 10.1016/j.biomaterials.2018.04.031.

[92] M. Deng, R. Yang, Q. Sun, J. Zhang, and J. Miao, "Small-molecule inhibitor HI-TOPK-032 improves NK-92MI cell infiltration into ovarian tumours," *Basic Clin. Pharmacol. Toxicol.*, vol. 134, no. 5, 2024, doi: 10.1111/bcpt.14002.