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Developing mRNA Vaccines towards Zika virus

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Abstract. All mRNA vaccines as a relatively newly developed branch of vaccine have shown a great prosperous future. Unique from the traditional vaccines, mRNA vaccines are fundamentally different in mechanism when promoting immunity for the body. This optimism is built on recently published studies demonstrating the efficacy of mRNA vaccines in combatting several types of cancer and infectious pathogens where conventional vaccine platforms may fail to induce protective immune responses. Traditional vaccines often contain a weakened or inactivated virus that our body can recognize as a real virus without putting us in danger, whereas the mRNA vaccine only carries out the instructions for our body to produce certain types of proteins that counter the virus. With the new Covid vaccine as a great representative, mRNA vaccines carry the genetic codes in messenger RNAs for proteins to recognize the need to build immunity for the virus. One of the most significant developments in progress includes the mRNA vaccine for Zika virus, a single-stranded RNA virus that can cause birth defects and is currently no cure or definite prevention. This review summarizes recent developments in mRNA vaccines from the past few years and discusses the challenges and future directions for the field.

Keywords: mRNA vaccines, Zika virus, Zika vaccines.

1. Introduction

1.1. Zika Virus

The single-stranded RNA Zika virus is typically spread by insects like mosquitoes and other bloodsucking flies. The primary negative impact on births and pregnancy is brain malfunction or microcephaly during the fetus's developmental stage. The host's symptoms are minor and not immediately apparent. Zika has had multiple significant outbreaks over the last ten years, and the World Health Organization designated the virus as a Public Health Emergency of International Concern in 2016 [1].

The 11-kilobase, non-segmented, positive-sense, single-stranded RNA genome of ZIKV is positive-sense. The single open reading frame (ORF) that encodes a single polyprotein is flanked by 5′ and 3′ untranslated regions in the genome. This polyprotein is cleaved into three structural proteins, and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5, and During maturation, the host furin protease cleaves prM inside the secretory route to generate M and pr. Pr is released from the virion when it leaves the cell and reaches the extracellular environment, which has a neutral pH [2,3]. E, the virus's primary antigenic determinant, mediates receptor binding and the fusion of the virus with the cell membrane after entry [4,5]. E is the antigen that most vaccinations target since it is the main target for

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neutralizing antibodies (nAbs) [6]. Non-infectious virus-like particles (VLPs), which have antigenic characteristics with infectious virions, are produced when prME is expressed in mammalian cells [7,8]. Important viral characteristics, such as fusogenic activity and the ability to elicit an antibody response, are retained by VLPs.

1.2. Current methods to counter Zika virus

Currently, medical treatment methods are limited to Zika virus, no antiviral treatments are available for the disease [9]. Main treatments for Zika focus on supportive and complementary actions, such as providing fluid, encouraging rest, or medicines for fever, soreness, or joint pains which could be side symptoms of Zika virus, such as Aspirin, or other anti-inflammatory drugs which can be used but only if the patient has been diagnosed, in order to avoid possible hemorrhage. People with symptoms such as rash, fever, or joint pain should get plenty of rest, drink fluids, and treat symptoms with antipyretics and/or analgesics.

No acute preventions exist either in front of Zika virus, and the only things that could be done include avoiding mosquitos and sexual transmissions, which is why developing a Zika virus vaccine is crucial. Pregnant women living in areas with Zika transmission or who develop symptoms of Zika virus infection should seek medical attention for laboratory testing, information, counseling, and other clinical care [10].

1.3. Why mRNA vaccines could be suitable for Zika virus

mRNA vaccines show promise as potential candidates for Zika virus prevention due to their adaptability and rapid development potential. These vaccines deliver genetic instructions for producing viral proteins, triggering a robust immune response without using live viruses. For Zika, mRNA vaccines could target the envelope protein, a key component for viral entry into cells. The flexibility of mRNA technology allows for quick modifications to address viral mutations, potentially providing broader protection against different Zika strains. Additionally, the relatively low-cost and scalable production of mRNA vaccines could facilitate widespread distribution in affected regions, crucial for controlling Zika outbreaks.

2. mRNA Vaccines for Zika Virus

2.1. Previous approaches for Zika virus vaccines

The development of vaccines for the Zika virus initially focused on DNA vaccines, with significant advancements noted around 2015 when congenital effects were documented. A diverse array of Zika virus vaccines was conceptualized, ranging from whole virus vaccines utilizing inactivated virus to peptide and protein-based vaccines. Although numerous vaccine models were created, only a limited number progressed to clinical trials, while the majority remained in theoretical or laboratory phases. The first vaccine to enter clinical trials was a DNA vaccine known as GLS-5700, which encodes the prME gene. Experiments conducted on mice demonstrated an immune response involving B cells and T cells targeting the virus's envelope. However, GLS-5700 was only able to offer protection against testicular and neuronal damage, as well as atrophy.

mRNA vaccines consist of synthetic mRNA molecules that instruct cells to produce antigens, thereby eliciting an immune response. In vitro-transcribed (IVT) mRNA replicates the structure of natural mRNA, comprising five components from 5′ to 3′: a 5′ cap, a 5′ untranslated region (UTR), an open reading frame encoding the antigen, a 3′ UTR, and a poly(A) tail. A variant of IVT mRNA, known as self-amplifying mRNA, includes replicase genes that code for RNA-dependent RNA polymerase. This polymerase, derived from viruses, amplifies mRNA transcripts within cells, facilitating the production of substantial amounts of antigen while minimizing the required mRNA dosage.

The 5′ cap structure, akin to that found in natural eukaryotic mRNAs, features a 7-methylguanosine nucleoside linked via a triphosphate bridge to the 5′ end of the mRNA. Similar to mammals, the first or second nucleotide from the 5′ end undergoes methylation at the 2′ hydroxyl of the ribose (2′-O-methylation), which inhibits recognition by cytosolic sensors of viral RNA, thereby averting unintended

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immune responses. Additionally, the 5′ cap provides steric protection against degradation by exonucleases and works in conjunction with the poly(A) tail at the 3′ end, along with poly(A) binding proteins.

2.2. mRNA-1325

Two experiments were carried out, one on mRNA-1325 (mRNA-1325 trial) and the other on mRNA-1893 (mRNA-1893 trial). Healthy adults between the ages of 18 and 49 were chosen for both, regardless of whether they had prior flavivirus infection. The mRNA-1325 trial involved randomly assigning people to one of three mRNA-1325 dosage groups (10, 25, or 100 μg) and one placebo group. The trial was conducted at three different locations in the USA. All individuals received two dosages. In order to incorporate the prME from a Zika virus strain from Micronesia in 2007, the mRNA-1325 vaccine was created. In the mRNA-1893 experiment, which was also carried out in three US locations and one in Puerto Rico, patients were randomized at random to either the placebo group or one. Two out of four dosage groups (10, 30, 100, or 250 μg) for mRNA-1893. In the mRNA-1893 experiment, each subject received a first dosage on day one and a second dose on day 29. Each study's main focus was safety, and assessments were conducted for the safety populations (trial participants in mRNA-1325 and mRNA-1893; participants in both trials received at least one dose and provided safety data), the solicited safety participants (trial participants in mRNA-1893; participants received at least one dose and provided solicited adverse reaction data), and the solicited safety populations (trial participants in mRNA-1893; participants received at least one dose and contributed solicited adverse reaction data). The investigation also examined the likelihood of negative reactions occurring seven days following

immunization and the reporting of side effects for a period of up to 28 days following vaccination. Both studies' secondary goals were to evaluate the immune response to the vaccine, with a focus on examining neutralizing antibodies (nAbs) specific to the Zika virus in the groups that satisfied the study's requirements (i.e., participants who did not significantly deviate from the study protocol received full doses of their assigned doses, had their samples collected within the designated timeframe, and provided serum samples for analysis both before and after the vaccination). These studies lacked rigorous hypothesis testing and were instead descriptive. Under the numbers NCT03014089 (mRNA-1325 study) and NCT04064905 (mRNA-1893 trial), both trials were registered on ClinicalTrials.gov. The trial for mRNA-1325 took place between December 14, 2016, and August 16, 2018. Ninety-one individuals were registered in total, with 53 (59%). Comprising 84 (93%) White people and 37 (41%) men; 82 (82%) were not Hispanic or Latino. All dose levels of mRNA-1325 (10, 25, and 100 μg) were generally well tolerated by the vaccine recipients; however, no significant neutralizing antibody (nAb) responses against the Zika virus were seen. The mRNA-1325 10 μg group showed the greatest geometric mean titers (GMTs) at 28 days following the second dosage.

2.3. mRNA-1893

The Brazilian RIO-U1 Zika virus isolate provides prME, which is encoded in this second-generation vaccine. After two doses that lasted for at least a year, mRNA-1893 was found to elicit significant Zika virus-specific nAb, according to a phase 1 trial. Participants in the study who were initially seropositive or seronegative for the flavivirus were also included. Based on the study's findings, all tested dosages had a good safety profile, suggesting that the vaccine is a good option to protect susceptible adult populations from contracting the Zika virus.

"Pregnancy-related Zika virus transmission protection remains a major unmet need, especially for pregnant women. The Fast Track designation validates our conviction on the clinical viability of mRNA-1893 and underscores the criticality of creating a vaccine that is efficacious and can be swiftly produced and implemented," stated Tal. Zaks, M.D., Ph.D., chief medical officer at Moderna. "Our Zika program is part of Moderna’s broader commitment to improving global public health through developing mRNA vaccines to prevent the spread of infectious diseases."

mRNA-1893 contains an mRNA sequence encoding for the structural proteins of Zika virus and is designed to cause cells to secrete virus-like particles, mimicking the response of the cell after natural

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infection. Preclinical data published in The Journal of Infectious Diseases have shown that vaccination with mRNA-1893 protected against transmission of Zika virus during pregnancy in mice. mRNA-1893 is currently in a Phase 1 study evaluating safety, pharmacokinetics, and pharmacodynamics in healthy volunteers [11].

2.4. ZIKV prM–E mRNA-LNP Vaccine

A versatile Zika virus could be generated as a platform such that particles could engulf genes that modify the messenger RNA instructions for both the variant and the wild type. This virus is not based on plasmids of DNA which utilizes a plasmid which is a small circular molecule that was made up of DNA molecules [12], introduced by the vaccines to trigger an immune response [13]. mRNA would not enter our genome which means no genetic information would be incorporated into our chromosomes, and foreign DNA integrating into our genes can lead to insertional mutagenesis and even oncogenesis [14]. mRNA vaccines are usually either non-amplifying or self-amplifying, which means that cellular responses are induced by a single dose. They are also known as replicons. The mRNA vaccine being produced for ZIKV prM-E contains a frame that codes the antigens and the 5'/3' areas that have not yet been translated and the translation is optimized on its efficiency. The mRNAs in ZIKV prM-E can stimulate immunity that appears innate, which could work better than protein vaccines. Since mRNA vaccines can be synthesized with almost any sequence provided, immunogens that code for mutations can be modified.

All three of the mRNA vaccines are antigen-specific neutralizing antibodies and adverse events, indicating their designed target of a specific pathogen, in order to prevent Zika and trigger an immune response. As they get injected, an antigen is brought in, and it mimics a certain part of the pathogen in our body. The antigen that was introduced by the vaccine would not be harmful, but would still be recognized as foreign, in our immune system. The vaccines stimulate an attack by foreign cells that carries infectious pathogens, in order to process and deliver those antigens to our T cells and B cells, which are crucial parts of our system for immunity. Antibodies will be made by B cells to target the antigen, and the antigens will get neutralized and marked for the destructive process. At the same time, T cells contribute to triggering a broader immune response by activating other immune cells. One of the fundamental elements of these antigen-specific vaccines comes from their ability to establish something called "immunological memory". It refers to the B cells and T cells that carry "memories" about the antigen, which would prepare them for an effective response if future contacts with the same type of antigen have been made, and they will be able to persist in our body.

2.5. Comparisons between types of vaccines

Conventional vaccines, which could be a weakened or deactivated virus sample, take longer to produce and tend to have more severe side effects, compared to RNA vaccines that could be manufactured rapidly using genetic information from pathogens. Thus, the mRNA vaccine has a high potential to be produced for protecting against Zika virus. They are more "body-friendly", effective, and also cheaper [15]. The level of safety of mRNA vaccines and their production is generally much higher compared to conventional vaccines such as whole virus vaccines. Leakages and accidents would have a less damaging effect on mRNA vaccines since they essentially contain merely coding instructions for proteins, whereas the conventional vaccines do contain real viruses, before the inactivation or weakened process.

One major difference between conventional vaccines and mRNA vaccines comes from the production time, as most traditional vaccines are made from viruses grown in chicken eggs or other mammal cells and the process of collecting samples of the virus is complex and challenging, including the adaptation for laboratory environment and transportation of the virus samples. RNA vaccines on the other hand are much more efficient in time needed for production or invention, as the mRNA which codes for antigens of the infectious agent, is made from a template of DNA in labs. The DNA sample can be generated from a digital sequence which could be sent anywhere instantly, which means the coding for the vaccine template is easily shared and transferrable.

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Another big difference is biosafety related to these two types of vaccines. Conventional vaccines require growing large quantities of the targeted virus in order to make the vaccine, which could result in potential hazards and infections. On the other hand, the RNA vaccines are synthesized solely from DNA templates, which has no harm to any. Only small amounts of the virus would be collected and used for gene sequencing as well as testing.

2.6. Antigen-specificity of mRNA vaccines

The antigen-specific vaccines are very important not only for the health of the individual but also for the community and the entire public health. When a portion of the population in the community gets vaccinated, the overall spread of the disease will be reduced and people who cannot be vaccinated can be more protected, since they also block the infections of the virus.

Potential adverse events may be applied with the usage of these vaccines. mRNA-1893 and mRNA-1325 use mild adverse events and they might include reactions at the injection part such as soreness, redness, or swelling. Other reactions could be systematic, such as fatigue, chills, mild headache, fevers, or muscle pain. These are considered the most common ones in adverse events, and more severe reactions could include allergies or inflammations of heart muscles. Particularly, there's a slight increase in records from young males being observed. mRNA vaccines could come with some adverse events but they're usually mild.

mRNA vaccines hold great promise for combating the Zika virus, a mosquito-borne pathogen that has caused significant concern due to its potential to cause birth defects and neurological complications. These vaccines use messenger RNA (mRNA) to instruct cells in the body to produce a viral protein, stimulating an immune response without using live viruses or causing disease. This innovative approach is highly effective in other viral infections, like COVID-19, and offers distinct advantages for Zika as well.

2.7. mRNA vaccines in general

2.7.1. Significance for Zika. One of the key benefits of mRNA vaccines for Zika virus is their rapid development and adaptability. Traditional vaccines, such as those based on weakened or inactivated viruses, often require long production times and complex manufacturing processes. In contrast, mRNA vaccines can be designed and produced more quickly, enabling a rapid response to emerging outbreaks. Given that Zika is most prevalent in tropical and subtropical regions, the speed of mRNA vaccine production could be crucial in containing sudden outbreaks.

Moreover, mRNA vaccines elicit a strong and precise immune response. They target the Zika virus's envelope protein, which is a critical component of the virus's structure. By generating antibodies specifically against this protein, the body is better prepared to recognize and neutralize the virus upon exposure. Importantly, mRNA vaccines do not carry the risk of causing infection, as no live virus is involved.

The flexibility of mRNA technology also allows for easier adjustments if the virus mutates, making it particularly suited for unpredictable viruses like Zika. Although clinical trials for mRNA vaccines against Zika are still in the early stages, the success of this platform in other infectious diseases underscores its potential to provide effective and lasting immunity against the Zika virus.

2.7.2. Prospects of mRNA vaccines. The future of mRNA vaccine development is incredibly promising, with the potential to revolutionize how we address a wide range of infectious diseases, cancers, and even autoimmune conditions. The success of mRNA vaccines during the COVID-19 pandemic demonstrated the platform's versatility and efficacy, and it has opened doors to a new era in vaccine technology. This innovative approach offers several advantages over traditional vaccines, including faster development timelines, adaptability to different pathogens, and a strong safety profile.

One of the most exciting prospects for mRNA vaccines is their potential to address pathogens for which no vaccines currently exist or where existing vaccines are inadequate. For instance, mRNA

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vaccines are being developed for challenging diseases like HIV, tuberculosis, and malaria. These diseases have proven difficult to target with conventional approaches, but mRNA technology offers a unique ability to stimulate precise immune responses by coding for specific antigens that are difficult to produce through traditional means. Additionally, the ability to rapidly design and test new mRNA vaccines means that emerging infectious threats, like future pandemics, can be responded to with unprecedented speed.

Beyond infectious diseases, mRNA vaccine technology is being explored for use in cancer immunotherapy. By instructing the body's cells to produce cancer-specific antigens, mRNA vaccines could help train the immune system to recognize and destroy tumor cells. This personalized approach holds immense potential for treating various types of cancer, as it can be tailored to target the unique mutations found in an individual's cancer cells.

Furthermore, mRNA vaccines may be used to treat or prevent autoimmune diseases by inducing tolerance to specific self-antigens, reducing harmful immune responses without suppressing overall immunity. As research progresses and technology advances, the flexibility and efficiency of mRNA platforms could transform medicine, offering new hope for diseases that have long eluded effective treatment.

3. Discussions

Synthesized mRNA vaccines proved itself as a great and prosperous type of vaccine. Cell-free manufacturing and clinical efficacies under fast developments, mRNA vaccines have displayed great advantages over the traditional vaccines that contain a sample of weakened or deactivated live virus, or protein-based subunit vaccine. Thus, they tend to get approved more easily, with an overall lower risk factor. The rapid development of mRNA vaccines also faces challenges such as even the administration doses that are usually high with adverse effects. The prerequisites of prime-boosted vaccines and the importance of an optimal storing environment should not be neglected. The difficulties could be overcome with the self-amplifying mRNAs in the next decade.

In contrast to m which only encodes a protein of interest, replicons have been engineered as a molecular chassis containing the gene of interest (GOI; transgene) and all required components for its self-amplification. The rapid amplification of replicon RNA in target cells increases the expression of the protein of interest (e.g., a viral (glycol)protein) and the induction of a protective immune response at a much lower initial RNA dose than conventional mRNA vaccines.2,3 The genes of self-amplifying replicons were derived from various families of positive-stranded RNA viruses. In this review, we focus on self-amplifying replicons derived from the alpha- and flavivirus family, regarding both human and veterinary applications.5,6 Because viral helical-shell structural genes were removed by the activation of the GOI, the replicon RNA cannot spread in the environment, in contrast to chimeric or recombinant virus vaccines.

Other main advantages of the replicon technology as compared with conventional vaccines include: first the nucleotide sequence of the transgene is synthetic, and since the replicon cannot spread, the manufacturing process of replicon vectors has low biocontainment restrictions compared with other viral vectors, and the injection of replicon technology into cellular membranes is safe-by-design. Second, due to the 'plug-and-play' character of replicons (the transgene simply has to be inserted), replicon technology can be easily applied in the event of emerging infectious disease outbreaks. Finally, the self-amplifying character of replicon technology can induce both humoral and cellular immune responses, which means that a single low-dose immunization should induce protective immunity. Although the biology is very well understood and several replicon technologies are available with distinct advantages over other vector technology, commercial application of alphavirus- and flavivirus-based replicons has just started. Here, we provide an overview of current challenges in replicon formulation and delivery and the safety considerations that need to be overcome. We discuss future opportunities for mucosal and therapeutic vaccination as well as novel advances in replicon design that can be exploited to transform this promising vaccine concept into a widely applied clinical platform technology.

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4. Conclusions

RNA vaccines are a prosperous type of vaccine that serves as a rapidly developing group for many viruses that haven't been invented with a vaccine. Zika virus poses a great threat to public health, has no existing vaccines produced but mRNA vaccines represented by mRNA-1893 and mRNA-1325, are currently developing vaccines in phase 2 and have great prospects for future Zika immunities. Similar to these two, ZIKV prM-E vaccines are making fast progress too into phase two trials. In the near future, we might be able to see them in the clinical trial period and eventually production.

Replicon formations of these developing mRNA vaccines are still facing challenges, but we provide an overview of current challenges in replicon formulation and delivery and the safety considerations that need to be overcome. The overall optimism of mRNA vaccine development is rational, and the mass production of Zika vaccines could be anticipated and witnessed in the near future. The functions of mRNA vaccines will be effective and sufficient, for their short production time, low risks, and efficiency. Some side effects might apply but most will remain minimal. Future opportunities for mucosal and therapeutic vaccination will be promising, as well as novel advances in replicon design that can be exploited to transform this promising vaccine concept into a widely applied clinical platform technology.

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