REVIEW

mRNA Vaccine—A Pioneer of COVID-19 Pandemic Termination

Miao Tan[1,2], Li Li[1,3], Tom Tang[1], Haitao Yang[1,4], Lei He[1], Qiang Hu[1,5]*

[1]Clinical and Regulatory Study Group. Chinese Biopharmaceutical Association, Potomac, MD, USA
[2]Pfizer Inc., La Jolla, CA, USA
[3]BLA Regulatory, LLC, Gaithersburg, MD. USA.
[4]Shenzhen Institute for the Research, Sun Yat-sen University, Shenzhen, China
[5]Hunter Medical LLC. Potomac, MD, USA

***Correspondence:**
Qiang Hu, M.D. Executive Chairman, Hunter Medical LLC. Potomac, MD, USA
Email: patrickhumd@yahoo.com.

ABSTRACT

Vaccines are one of the major success stories of modern medicine. The development of vaccines progressed at a fairly slow rate until the last decade when new scientific discoveries and technologies led to innovative gene-based vaccines. Gene-based vaccines are a completely new type of vaccine that are faster and cheaper to produce than traditional vaccines. mRNA vaccines use a different approach that takes advantage of processes that are more efficient, cost-effective and safe. On the basis of these remarkable properties, mRNA vaccines quickly moved forward and within ten years were being used in some early clinical trials for infectious diseases and several types of cancer. The COVID-19 outbreak dramatically accelerated mRNA vaccines, moving them from development to authorized use in a record-setting ten months. In this review, we provide an overview of mRNA vaccine development and its application against the COVID-19 pandemic. As the first approved COVID vaccines, mRNA vaccines have been shown to be safe and mRNA technology will have a tremendous impact, not only on the pandemic, but also on the future treatment of many diseases [Am J Transl Med 2021. 5 (1): 13-24].

Keywords: SARS-CoV-2, mRNA, Vaccine, COVID-19

(Manuscript received February 1, 2021, accepted February 21, 2020; published online March 1, 2021)

INTRODUCTION

The practice of vaccination started with Edward Jenner in 1796. Since then, vaccines have helped billions of people avoid illnesses and have saved

© Hawaii Gangze Inc., Publisher, Honolulu, USA

numerous lives. The progress in biology and molecular technology has meant that vaccines could be made in laboratories in the 19th century, were produced based on immunologic markers in the 20th century, and even use genetic materials in the 21st century (Plotkin, 2014). There are two types of vaccines, based on their development: conventional vaccines and genetically engineered vaccines. Traditional vaccines consist of inactivated partly or fully purified proteins harvested from growing the microorganism (virus or bacteria). The revolution of genetic engineering toward the end of the 20th century has greatly impacted vaccine development. The first fruit of that revolution was the vaccine against hepatitis B. Valenzuela et al. (1982) placed the coding sequence for the S antigen into yeast cells and were able to produce large quantities of surface-antigen particles in vitro. Genetically engineered vaccines are more costly to manufacture than conventional vaccines, and the antigens can be purified to a higher standard than was demanded of older, conventional vaccines. Since then, genetic engineering has been used to produce many candidate antigens for vaccines in yeast, animal cells, or insect cells, producing an antigen in culture. However, these protein-based vaccines need to use adjuvants to improve vaccine immunogenicity. Unfortunately, the mechanisms of adjuvant toxicity are less well understood. The most challenging aspect of assessing adjuvant risk is determining the basis of reported associations between the use of vaccines containing specific adjuvants and the development of rare autoimmune or chronic degenerative disorders (Petrovsky, 2015).

GENE-BASED VACCINE: mRNA AND DNA VACCINES

The gene-based vaccine immediately evoked the interest of an increasing number of authors when Wolff et al. (1990) demonstrated that direct injection of in vitro transcribed (IVT) mRNA or plasmid DNA (pDNA) into the skeletal muscle of mice led to the expression of the encoded protein in the injected muscle. The gene-based vaccine involves the direct introduction of a DNA or RNA sequence encoding the antigen or antigens against which an immune response is sought, and relies on the *in situ* production of the target antigen. This means that the cell's machinery uses the instructions contained in the introduced genetic material to make virus antigens that the immune system reacts to. This approach offers a number of potential advantages over traditional approaches, including the stimulation of both B- and T-cell responses, improved vaccine stability, the absence of any infectious agent and the relative ease of large-scale manufacture (WHO, n.d.). Moreover, DNA- or RNA-based vaccines may even be effective against non-infectious conditions such as cancer and autoimmune diseases, where conventional vaccines are ineffective. Gene-based vaccines have been shown to generate immune responses against such viral diseases as influenza, hepatitis B, human immunodeficiency (HIV), and rabies, as well as against malarial parasites, among others, in animals. With a gene-based vaccine boom taking place worldwide, the field of DNA vaccination was developing rapidly by the early- to mid-1990s, but the same was not true of mRNA vaccination because of mRNA's instability, high innate immunogenicity and inefficient in vivo delivery. In the early 2000s, biochemist Katalin Karikó happened across a study which showed that one of mRNA's nucleotides, Uridine, could trigger certain immune receptors. It was the crucial piece of information she had been searching for. In 2005, Karikó and Weissman published a study announcing a specifically modified form of mRNA, which replaced Uridine with an analog – a molecule which looked the same but did not induce an immune response (Karikó & Weissman,

© Hawaii Gangze Inc., Publisher, Honolulu, USA

2012, 2014). An added challenge in obtaining clinical approval for mRNA vaccines is their intracellular delivery. mRNA is highly unstable under physiological conditions, and naked mRNA is not able to be delivered into cells. Several strategies have been developed for RNA delivery, including RNA-conjugates, modified RNA, viral vectors and microparticles and nanoparticles (Reichmuth et al., 2016). To protect mRNA against degradation by nucleases and shield its negative charge, amine-containing materials are commonly used as non-viral vectors. One of the most developed methods for mRNA delivery is co-formulation into lipid nanoparticles (LNPs). Although the mechanism of mRNA delivery by the LNPs is not fully understood, it is generally accepted that these multicomponent LNPs are taken up by endocytosis and can electrostatically attach and fuse with the cell membrane using inverted non-bilayer lipid phases (Kowalski et al., 2019). Over the past decade, major technological innovation and investment in research have enabled mRNA to become a promising therapeutic tool in the fields of vaccine development and protein replacement therapy.

There are several important differences between IVT mRNA-based therapeutic approaches and other nucleic acid-based therapies. IVT mRNA does not need to enter into the nucleus to be functional; once it has reached the cytoplasm, the mRNA is translated instantly. By contrast, DNA therapeutics need to access the nucleus to be transcribed into RNA, and their functionality depends on nuclear envelope breakdown during cell division. In addition, IVT mRNA-based therapeutics, unlike plasmid DNA and viral vectors, do not integrate into the genome and therefore do not pose the risk of insertional mutagenesis. For most pharmaceutical applications, it is also advantageous that IVT mRNA is only transiently active and is completely degraded via physiological metabolic pathways. Moreover, the production of IVT mRNA is relatively simple and inexpensive, and so the development of IVT mRNA-based therapeutics has garnered broad interest (Sahin et al., 2014). Finally, this lack of genomic integration, in combination with mRNA being non-replicative as well as metabolically decaying within a few days, makes mRNA a merely transient carrier of information and offers strong safety advantages (Pascolo, 2006; Jäschke & Helm, 2003; Chetverin, 2004; Probst et al., 2007).

The manufacturing process of mRNA in vitro synthesis and modification begins with the generation of a plasmid DNA (pDNA) containing a DNA-dependent RNA polymerase promoter and the corresponding sequence for the mRNA construct. In vitro transcription technology of mRNA is mature, and the most popular method is using T3, T7, or SP6 RNA polymerase and linear DNA (linearized plasmid DNA or synthetic DNA prepared by PCR) for mRNA synthesis. There are some basic structural elements of mature mRNA in the eukaryote that are required to keep mRNA functional, including the five-prime cap (5' cap), the five-prime untranslated region (5' UTR), an open reading frame (ORF) region, the three-prime untranslated region (3' UTR), and the poly (A) tail structure. Keeping mRNA structure intact is beneficial for mRNA stability and expression capability. Modifying the mRNA sequence based on its complete structure can further optimize the efficiency of an mRNA vaccine. However, the initial product of mRNA in vitro transcription is the mixture of targeted mRNA, untargeted RNA, nucleotides, oligodeoxynucleotides, and proteins. To purify the mRNA, precipitation and extraction techniques are used to remove common impurities, and chromatographic techniques are generally used to separate the target mRNA from other mRNA impurities in this system (Jackson et al., 2020; Schlake et al., 2012; Xu et al., 2020; Zeng et al., 2020).

© Hawaii Gangze Inc., Publisher, Honolulu, USA

The mRNA vaccine field is developing extremely rapidly; a large body of preclinical data has accumulated over the past several years, and more than 70 mRNA vaccines have been initiated for human clinical trials. Pardi et al. (2018) discussed current mRNA vaccine approaches, summarized the latest findings, highlighted challenges and recent successes, and offered perspectives on the future of mRNA vaccines. The data suggest that mRNA vaccines have the potential to solve many of the challenges in vaccine development for both infectious diseases and cancer. However, all of these mRNA vaccines were stuck at early clinical trials until the COVID-19 pandemic spread throughout the world in 2020.

COVID-19 mRNA VACCINES

DEVELOPMENT

In December 2019, an outbreak of an unknown pneumonia started in Wuhan, China. By January 2020, the etiologic agent had been isolated and identified as a novel coronavirus (Bishara et al, 2020; Huang et al., 2020; Zhu et al., 2020; Zhou et al., 2020). Within a month, the genetic sequence of the virus became available (MN908947.3) (Wu et al., 2020). Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11th, 2020, mainly due to the speed and scale of the transmission of the disease (WHO, n.d.). Later, the International Committee on Taxonomy of Viruses officially designated the virus as SARS-CoV-2, based on phylogeny, taxonomy and established practice (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). As of

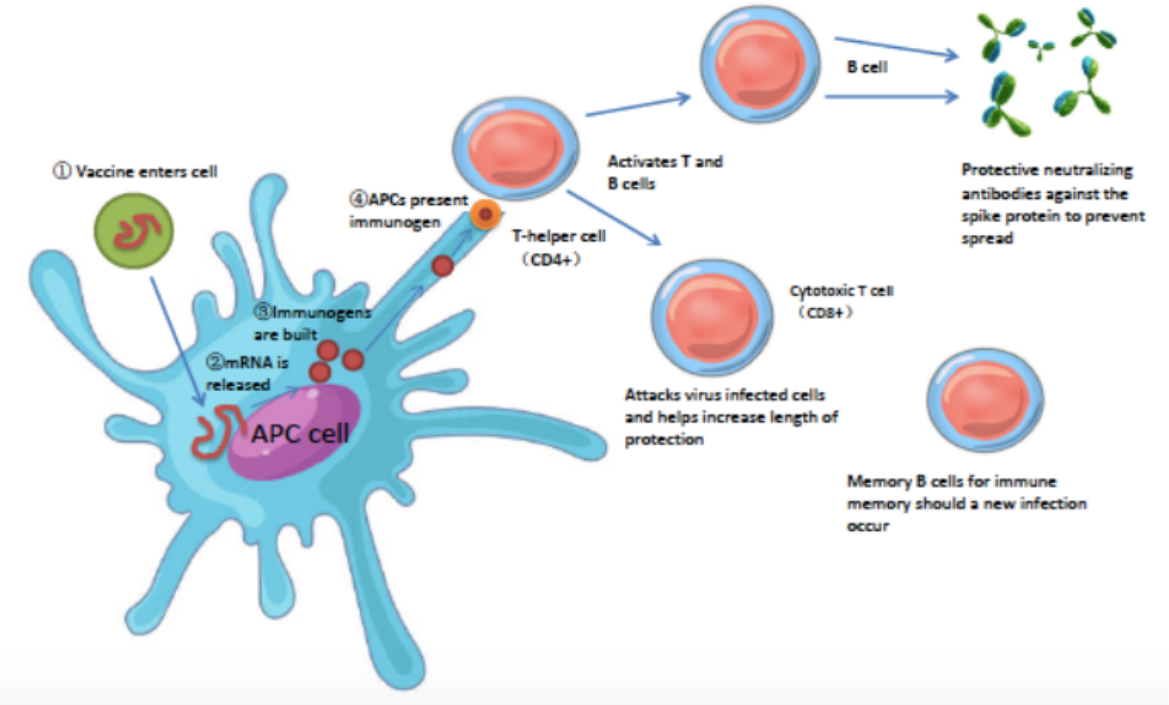

Figure 1: Mechanism of COVID-19 mRNA Vaccine against viral infection

© Hawaii Gangze Inc., Publisher, Honolulu, USA

January 7, 2021, more than 88 million confirmed infection cases and 1.9 million deaths had been reported across the world (Johns Hopkins University, n.d.). No vaccines were available to prevent COVID-19 infection until December 11, 2020, when the U.S. Food and Drug Administration issued the first emergency use authorization for a vaccine for the prevention of COVID-19 (FDA, 2020). The mechanism of the COVID-19 mRNA vaccine against viral infection is summarized in **Figure 1**.

SARS-CoV-2 is a single-stranded RNA-enveloped virus. Gene fragments express structural and nonstructural proteins. Coronaviruses consist of four structural proteins: the nucleocapsid protein (N) forms the helical capsid to accommodate its genome. The whole structure is further surrounded by a lipid envelope, which is made of S (spike), E (envelope) and M (membrane) proteins. The receptor-binding subunits S1 and S2 are placed in the ectodomain region. During infection, the S1 binds with the host receptor (ACE2), and S2 fuses the host and viral membranes, thereby releasing the viral genome into the cell (Y. Huang et al., 2020; Bangaru et al., 2020). The trimeric spike glycoprotein (S) of SARS-CoV-2 is a key target for vaccines, therapeutic antibodies, and diagnostics. It binds ACE2 with higher affinity than does severe acute respiratory syndrome (SARS-CoV). The C-terminal furin cleavage fragment (S2) contains the fusion machinery. Membrane fusion can be blocked by mutating S residues 986 and 987 to prolines, producing an S antigen stabilized in the prefusion conformation (P2 S). The RBD is a key target for virus neutralizing antibodies, with an 'up' conformation, in which more neutralizing epitopes are exposed, and a 'down' conformation, in which many epitopes are buried. In addition, some neutralizing antibodies bind S epitopes outside the RBD (Wrapp et al., 2020; Yang et al., 2020; Chi et al., 2020).

In January 2020, after reading an article in Lancet about a new coronavirus in China, Ugur Sahin, a founder of BioNTech, quickly made the decision to develop an mRNA vaccine against the virus. BioNTech is a German biotechnology company that develops pharmaceutical candidates based on mRNA for use as individualized cancer immunotherapies, as vaccines against infectious diseases and as protein replacement therapies for rare diseases. BioNTech launched a crash project to devise a vaccine based on RNA sequences and made a deal with Pfizer in March to develop it together. The two companies had been working together since 2018 to develop flu vaccines using mRNA technology (Isaacson, n.d.). Moderna, another mRNA vaccine development company based in Cambridge, MA, went to work on the virus vaccine almost at same time, as soon as the Chinese government posted the virus's sequence.

As of 8 April 2020, the global COVID-19 vaccine R&D landscape includes 115 vaccine candidates (Le et al., 2020). A striking feature of the vaccine development landscape for COVID-19 is the range of technology platforms being evaluated, including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches.

BNT162b2, the COVID mRNA vaccine from Pfizer/BioNTech, encodes P2 S that authentically presents the ACE2 binding site and other epitopes targeted by SARS-CoV-2 neutralizing antibodies with a native furin cleavage site, resulting in the S1 and S2 cleavage fragments. The m1Ψ-modification dampens innate immune sensing and, together with optimized non-coding sequence elements, increases RNA translation in vivo. BNT162b2 RNA in vitro transcribed by T7 polymerase from a plasmid DNA template has a single, sharp-peak microfluidic capillary electrophoresis profile, consistent with its

© Hawaii Gangze Inc., Publisher, Honolulu, USA

calculated length of 4,283 nucleotides, indicating purity and integrity. When HEK293T/17 cells were incubated with BNT162b2 (which is LNP-formulated) or with BNT162b2 RNA mixed with a transfection reagent, robust expression of P2 S was detectable by flow cytometry. To characterize BNT162b2-elicited B- and T-cell responses, BALB/c mice were immunized intramuscularly (IM) once with 0.2, 1, or 5 μg BNT162b2 or received a buffer control. S1- and RBD-binding serum IgG developed rapidly at all dose levels in a dose-dependent manner. For S1-binding antibodies, the geometric mean concentration (GMC) in the 5-μg group was 386μg/mL at Day 28. At Day 28 after immunization, vaccine-elicited IgG had a strong binding affinity for S1 (geometric mean KD 12 nM) and the RBD (geometric mean KD 0.99 nM), with both having a low off-rate. A high fraction of splenocytes of $CD4^+$ and CD^{8+} T-cell phenotype isolated from mice on Days 12 and 28 after BNT162b2 immunization had a strong antigen-specific IFNγ and IL-2 response and also elicited S-specific $IFN\gamma^+$ producing $CD8^+$ 162 T cells. (Vogel et al., 2020) The mRNA-1273, a Moderna-developed mRNA COVID vaccine, stimulated SARS-CoV-2 S-2P–specific antibody responses in rhesus macaques. IgG binding to the conformationally defined prefusion S-2P protein was increased over baseline in a dose-dependent manner after two vaccinations. Serum from animals in the 100-μg dose group had inhibition of ACE2 binding to the receptor-binding domain that was 938 times as high as that in serum from animals in the control group. The SARS-CoV-2–specific T-cell immunity that may have a role in pathogenesis or protection against SARS-CoV-2 also tested in vaccinated animals. A dose-dependent increase in Th1 responses was noted 4 weeks after the second vaccination, but CD8 T-cell responses were low to undetectable (Corbett et al., 2020).

The development of a new vaccine typically takes 10-15 years (Sharma et al., 2020). However, the BNT162b2 and mRNA-1273 took only about 11 months. It is clearly a challenge to develop a vaccine against COVID-19 in such a short time, and more details of de novo, in vitro, and in vivo data are needed. Fortunately, a series phase I/II research of different targets of mRNA vaccines demonstrated that they are safe for humans. Pfizer and Moderna confidently pulled their mRNA vaccines into clinical trials. In the BNT162b2 phase I/II study, 76 subjects were screened, and 45 participants were randomized and vaccinated (Mulligan et al., 2020a; 2020b). Robust immunogenicity was observed after vaccination with BNT162b1. RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers were increased dramatically in all of the dose groups after the second dose of BNT162b1. Sera were obtained before immunization (Day 1) and 7, 21, and 28 days after the first immunization. Human COVID-19 convalescent sera (HCS, n=38) were obtained at least 14 days after PCR-confirmed diagnosis and at a time when the donors were asymptomatic. Geometric mean concentrations (GMCs) of day 35, 14 days after the second dose, were 5,880-16,166 U/mL compared to 602 U/mL in the HCS. Greater serum neutralizing GMTs were achieved 7 days after the second 10 μg or 30 μg dose, reaching 168-267, compared to 94 for the HCS. The kinetics and durability of neutralizing titers are being monitored. The BNT162b1 exhibited a tolerability and safety profile consistent with those previously observed for mRNA-based vaccines. A clear dose-level response in elicited neutralizing titers was observed after doses 1 and 2 in participants, with a particularly steep dose response between the 10-μg and 30-μg dose levels. The most common systemic events reported in the 7 days after each vaccination in both BNT162b1 and placebo recipients were mild to moderate fatigue and headache. Reports of fatigue and headache were more common in the BNT162b1 groups compared to the placebo group. Additionally, chills, muscle pain, and joint pain were reported among BNT162b1 recipients and not among placebo

© Hawaii Gangze Inc., Publisher, Honolulu, USA

recipients. Two participants reported a severe adverse event: Grade 3 pyrexia 2 days after vaccination in the 30-μg group, and sleep disturbance 1 day after vaccination in the 100-μg group. No Grade 1 or greater change in routine clinical laboratory values or laboratory abnormalities were observed for most subjects after either of the BNT162b1 vaccinations. The most common changes were decreases in lymphocyte count after vaccine administration. One participant each in the 10-μg group (8.3% [1/12]) and the 30-μg group (9.1% [1/11]) dose levels and 4 participants at the 100-μg group (33.3% [4/12]) had Grade 3 decreases in lymphocytes. These post Dose 1 decreases in lymphocyte count were transient and levels returned to normal 6-8 days after vaccination. None of the postvaccination abnormalities observed were associated with clinical findings. mRNA-1273, which induces immunity to SARS-CoV-2 by encoding S protein, also displayed immune responses in all participants. After the second vaccination, the titers increased (day 57 GMT, 299,751, 782,719, and 1,192,154, respectively) (L. A. Jackson et al., 2020). No serious adverse events were reported, and no prespecified trial-halting rules were met. The most common solicited adverse events were headache, fatigue, myalgia, chills, and injection-site pain. Three participants had erythema that lasted for 5 to 7 days; all the cases were mild and began on Day 1 or 2. One participant had mild myalgia symptoms that began on Day 3 and lasted for 5 days. Two solicited systemic adverse events that were classified as severe (grade 3) occurred after the second dose: fever in a participant between the ages of 56 and 70 years in the 25-μg dose subgroup and fatigue in a participant who was 71 years of age or older in the 100-μg dose subgroup (Anderson et al., 2020).

After getting safety and efficacy data of phase I/II trails, Pfizer and Moderna started a large number of participants in ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy phase III trials on April 29, 2020 and July 27, 2020. A total of 43,548 participants underwent randomization, of whom 43,448 received injections, 21,720 with BNT162b2 and 21,728 with a placebo. There were 8 cases of COVID-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to the placebo; BNT162b2 was 95% effective in preventing COVID-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe COVID-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups (Polack et al., 2020). For its phase III trial, Moderna enrolled 30,420 volunteers, who were randomly assigned in a 1:1 ratio to receive either the vaccine or a placebo (15,210 participants in each group). More than 96% of participants received both the first and second doses, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic COVID-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; $p < 0.001$). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe COVID-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity

© Hawaii Gangze Inc., Publisher, Honolulu, USA

after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups (Baden et al., 2020).

ADVERSE EFFECTS FROM THE COVID-19 VACCINATION DEVELOPMENT

Serious adverse effects from the COVID-19 vaccination seem extremely rare. Bell's palsy was noted more often in mRNA vaccinated patients than in those who received a placebo in both BNT162b1 and mRNA-1273. The usual incidence of Bell`s palsy is 15-30/100,000/year. The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and an association between COVID-19 and Bell's palsy has been reported. Severe allergic reactions, including possible anaphylaxis, have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials (WHO, 2020). Anaphylaxis is a known, but rare, side effect with any vaccine. The mild side effects of COVID-19 mRNA vaccines include fatigue (9.7%), muscle pain (8.9 %), joint pain (5.2 %), and headache (4.5 %) (Wadman, 2020), similar to those of flu vaccines (WHO, 2012). Recently, there have been reports of 23 deaths in Norway of people who received the COVID-19 vaccine from Pfizer/BioNTech. The Norwegian Medicines Agency concluded that common adverse reactions to mRNA vaccines, including fever and nausea, could have contributed to deaths in elderly and frail patients (Buntz, 2021). Officials in the U.S. are also investigating the death of a physician in Florida who developed a blood disorder after receiving the Pfizer-BioNTech vaccine. California's top doctor is recommending a pause on distributing a specific batch of COVID-19 vaccinations that was linked to several allergic reactions in downtown San Diego on January 18 (BNC 7, n.d.). It will take time and large numbers of people getting vaccinated before more is known about possible adverse effects. Safety monitoring will continue even after a COVID-19 vaccine is approved. Recently, several new COVID-19 variants have been found in the UK, Brazil, and South Africa. New variants may increase virus spread, induce immune escape, or reduce monoclonal antibodies combating the virus. How these new variants are affecting the course of the pandemic is still unclear (Kupferschmidt, 2021, & Pm, 2021). The Pfizer/BioNTech BNT162b1 vaccine is protective against the UK and the Brazilian new strains, according to the preliminary results of a Pfizer study. If vaccine-resistant SARS-CoV-2 strains emerge, vaccines might need to be updated. Fortunately, Lavine et al.'s (2021) analysis of immunological and epidemiological data on endemic human coronaviruses shows that infection-blocking immunity wanes rapidly, but disease-reducing immunity is long-lived. They suggest that the pandemic may be no more virulent than the common cold and predict that once the endemic state is reached, mass vaccination may no longer be necessary to save lives. Several other COVID-19 mRNA vaccines are undergoing clinical trials in different countries (NIH, 2021).

SUMMARY AND FUTURE PERSPECTIVES

The mRNA vaccine is a great achievement in modern public health that has considerable advantages over conventional vaccines, including simplicity of design and synthesis, fast manufacturing for a rapid and

© Hawaii Gangze Inc., Publisher, Honolulu, USA

effective epidemic response, and affordability for numerous populations. Based on these properties, it was immediately used in the fight against the COVID-19 virus that caused a pandemic beginning in December 2019. The COVID-19 pandemic is the defining global health crisis of our time and the greatest challenge we have faced since World War II. However, the pandemic is much more than a health crisis, it is also an unprecedented socio-economic crisis. While COVID-19 mRNA vaccines are being developed as quickly as possible, routine processes and procedures remain in place to ensure the safety of any vaccine that is authorized or approved for use. We will continue to learn how well the vaccines work and how best to use them. As new information is incorporated into our decision making, we will need to make it a priority to be clear and transparent about what we do and do not know (Subbarao, 2020). The success of an mRNA vaccine in fighting the COVID pandemic is the first step in demonstrating its powerful properties. If using mRNA as a medicine works for one disease, it should work for many diseases. The mRNA as a therapeutic agent could be a great help for patients suffering from monogenic diseases. The flexibility and variability of proteins that can be replaced by the cell's own translational machinery through the use of mRNA is nearly unlimited. This makes mRNA a unique therapeutic molecule, which is poised to revolutionize therapeutic options for patients in the coming years.

.

REFERENCES

Anderson, E. J., Rouphael, N. G., Widge, A. T., Jackson, L. A., Roberts, P. C., Makhene, M., Chappell, J. D., et al. (2020). Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. New England Journal of Medicine, 383(25), 2427–2438. Massachusetts Medical Society.

Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., et al. (2020). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. New England Journal of Medicine, 0(0), null. Massachusetts Medical Society.

Bangaru, S., Ozorowski, G., Turner, H. L., Antanasijevic, A., Huang, D., Wang, X., Torres, J. L., et al. (2020). Structural analysis of full-length SARS-CoV-2 spike protein from an advanced vaccine candidate. Science (New York, N.Y.), 370(6520), 1089–1094.

Bishara C, Sidime F, Bass J, Blaize J. (2020). Could certain strains of gut bacteria play a role in the prevention and potential treatment of COVID-19 infections? American Journal of Translational Medicine 2020. 4(2): 75-94.

BNC 7. (n.d.). Calif Urges Stop on 1 Vaccine Batch After Allergic Reactions in San Diego. NBC 7 San Diego. Retrieved January 18, 2021, from https://www.nbcsandiego.com/news/local/states-top-doctor-recommends-covid-19-vaccine-providers-pause-certain-batch-after-allergic-reactions-at-tailgate-park/2498536/

Buntz, B. (2021, January 15). Norway investigating deaths of 23 individuals who received COVID-19 vaccine. Drug Discovery and Development. Retrieved January 18, 2021, from https://www.drugdiscoverytrends.com/norway-investigating-deaths-of-23-individuals-who-took-covid-19-vaccine/

Chetverin, A. B. (2004). Replicable and recombinogenic RNAs. FEBS letters, 567(1), 35–41.

Chi, X., Yan, R., Zhang, J., Zhang, G., Zhang, Y., Hao, M., Zhang, Z., et al. (2020). A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. Science, 369(6504), 650–655. American Association for the Advancement of Science.

Corbett, K. S., Flynn, B., Foulds, K. E., Francica, J. R.,

© Hawaii Gangze Inc., Publisher, Honolulu, USA

Boyoglu-Barnum, S., Werner, A. P., Flach, B., et al. (2020). Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. New England Journal of Medicine, 383(16), 1544–1555. Massachusetts Medical Society.

Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. (2020). The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology, 5(4), 536–544.

FDA. (2020, December 11). EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19). Retrieved from https://www.fda.gov/media/144413/download

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England), 395(10223), 497–506.

Huang, Y., Yang, C., Xu, X.-F., Xu, W., & Liu, S.-W. (2020). Structural and functional properties of SARS-CoV-2 spike protein: Potential antivirus drug development for COVID-19. Acta Pharmacologica Sinica, 41(9), 1141–1149.

Isaacson, W. (n.d.). How mRNA Technology Could Upend the Drug Industry. Time. Retrieved January 13, 2021, from https://time.com/5927342/mrna-covid-vaccine/

Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., et al. (2020). An mRNA Vaccine against SARS-CoV-2—Preliminary Report. New England Journal of Medicine, 383(20), 1920–1931. Massachusetts Medical Society.

Jackson, N. A. C., Kester, K. E., Casimiro, D., Gurunathan, S., & DeRosa, F. (2020). The promise of mRNA vaccines: A biotech and industrial perspective. NPJ vaccines, 5, 11.

Jäschke, A., & Helm, M. (2003). RNA sex. Chemistry & Biology, 10(12), 1148–1150.

Johns Hopkins University. (n.d.). Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center. Retrieved January 11, 2021, from https://coronavirus.jhu.edu/

Kariko, K., & Weissman, D. (2012, October 2). RNA containing modified nucleosides and methods of use thereof. U.S. Patent US8278036B2. Washington, DC: U.S. Patent and Trademark Office.

Kariko, K., & Weissman, D. (2014, June 10). RNA containing modified nucleosides and methods of use thereof. U.S. Patent US8748089B2. Washington, DC: U.S. Patent and Trademark Office.

Kowalski, P. S., Rudra, A., Miao, L., & Anderson, D. G. (2019). Delivering the Messenger: Advances in Technologies for Therapeutic mRNA Delivery. Molecular Therapy, 27(4), 710–728.

Kupferschmidt, K., 2021, & Pm, 4:55. (2021, January 15). New coronavirus variants could cause more reinfections, require updated vaccines. Science | AAAS. Retrieved January 20, 2021, from https://www.Sciencemag.org/news/2021/01/new-coronavirus-variants-could-cause-more-reinfections-require-updated-vaccines

Lavine, J. S., Bjornstad, O. N., & Antia, R. (2021). Immunological characteristics govern the transition of COVID-19 to endemicity. Science. American Association for the Advancement of Science. Retrieved January 18, 2021, from https://science.sciencemag.org/content/early/2021/01/11/science.abe6522

Le, T. T., Andreadakis, Z., Kumar, A., Román, R. G., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. Nature

© Hawaii Gangze Inc., Publisher, Honolulu, USA

Reviews Drug Discovery, 19(5), 305–306.

Mulligan, M. J., Lyke, K. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., et al. (2020a). Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature, 586(7830), 589–593.

Mulligan, M. J., Lyke, K. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., et al. (2020b). Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. MedRxiv, 2020.06.30.20142570. Cold Spring Harbor Laboratory Press.

NIH. (2021, January 20). Clinical Trials of COVID19 Vaccines. U.S. National Library of Medicine. Retrieved fromhttps://www.clinicaltrials.gov/ct2/results?cond=covid19+vaccine&term=&cntry =&state=&city=&dist=

Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines—A new era in vaccinology. Nature Reviews. Drug Discovery, 17(4), 261–279.

Pascolo, S. (2006). Vaccination with messenger RNA. Methods in Molecular Medicine, 127, 23–40.

Petrovsky, N. (2015). Comparative Safety of Vaccine Adjuvants: A Summary of Current Evidence and Future Needs. Drug Safety, 38(11), 1059–1074.

Plotkin, S. (2014). History of vaccination. Proceedings of the National Academy of Sciences, 111(34), 12283–12287. National Academy of Sciences.

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., et al. (2020). Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. New England Journal of Medicine, 383(27), 2603–2615. Massachusetts Medical Society.

Probst, J., Weide, B., Scheel, B., Pichler, B. J., Hoerr, I., Rammensee, H.-G., & Pascolo, S. (2007). Spontaneous cellular uptake of exogenous messenger RNA in vivo is nucleic acid-specific, saturable and ion dependent. Gene Therapy, 14(15), 1175–1180.

Reichmuth, A. M., Oberli, M. A., Jaklenec, A., Langer, R., & Blankschtein, D. (2016). MRNA vaccine delivery using lipid nanoparticles. Therapeutic Delivery, 7(5), 319–334.

Sahin, U., Karikó, K., & Türeci, Ö. (2014). mRNA-based therapeutics—Developing a new class of drugs. Nature Reviews Drug Discovery, 13(10), 759–780. Nature Publishing Group.

Schlake, T., Thess, A., Fotin-Mleczek, M., & Kallen, K.-J. (2012). Developing mRNA-vaccine technologies. RNA biology, 9(11), 1319–1330.

Sharma, O., Sultan, A. A., Ding, H., & Triggle, C. R. (2020). A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Frontiers in Immunology, 11. Frontiers. Retrieved January 16, 2021, fromhttps://www.frontiersin.org/articles/10.3389/fimmu.2020.585354/ full?utm_source=F-AAE&utm_ medium=EMLF&utm_campaign=MRK_1463957_35_Immuno_20201022_arts_A

Subbarao, K. (2020). COVID-19 vaccines: Time to talk about the uncertainties. Nature, 586(7830), 475–475. Nature Publishing Group.

Valenzuela, P., Medina, A., Rutter, W. J., Ammerer, G., & Hall, B. D. (1982). Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature, 298(5872), 347–350.

Vogel, A. B., Kanevsky, I., Che, Y., Swanson, K. A., Muik, A., Vormehr, M., Kranz, L. M., et al. (2020). A prefusion SARS-CoV-2 spike RNA vaccine is highly immunogenic and prevents lung infection in non-human primates. BioRxiv, 2020.09.08.280818. Cold Spring Harbor Laboratory.

© Hawaii Gangze Inc., Publisher, Honolulu, USA

Wadman, M. (2020). Public needs to prep for vaccine side effects. Science, 370(6520), 1022–1022. American Association for the Advancement of Science.

WHO. (2012, July). INFORMATION SHEET OBSERVED RATE OF VACCINE REACTIONS INFLUENZA VACCINE. WHO. Retrieved from https://www.who.int/vaccine_safety/initiative/tools/Influenza_Vaccine_rates_information_sheet.pdf

WHO. (2020, December 22). mRNA vaccines against COVID-19: Pfizer-BioNTech COVID-19 vaccine BNT162b2. WHO. Retrieved from file:///C:/ Users/ mtan/Downloads/WHO-2019-nCoV-vaccinesSAGE_ evaluation-BNT162b2-2020.1-eng.pdf WHO. (n.d.). Listings of WHO's response to COVID-19. Retrieved January 8, 2021a, from https://www.who.int/news/ item/29-06-2020-covidtimeline

WHO. (n.d.). Naming the coronavirus disease (COVID-19) and the virus that causes it. Retrieved January 11, 2021b, from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

Wolff, J. A., Malone, R. W., Williams, P., Chong, W., Acsadi, G., Jani, A., & Felgner, P. L. (1990). Direct gene transfer into mouse muscle in vivo. Science (New York, N.Y.), 247(4949 Pt 1), 1465–1468.

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C.-L., Abiona, O., Graham, B. S., et al. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science, 367(6483), 1260–1263.

Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Song, Z.-G., Hu, Y., et al. (2020). A new coronavirus associated with human respiratory disease in China. Nature, 579(7798), 265–269.

Xu, S., Yang, K., Li, R., & Zhang, L. (2020). MRNA Vaccine Era-Mechanisms, Drug Platform and Clinical Prospection. International Journal of Molecular Sciences, 21(18).

Yang, J., Wang, W., Chen, Z., Lu, S., Yang, F., Bi, Z., Bao, L., et al. (2020). A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. Nature, 586(7830), 572–577.

Zeng, C., Zhang, C., Walker, P. G., & Dong, Y. (2020). Formulation and Delivery Technologies for mRNA Vaccines. Current Topics in Microbiology and Immunology.

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270–273.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., et al. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England Journal of Medicine, 382(8), 727–733.

© Hawaii Gangze Inc., Publisher, Honolulu, USA