Evaluating the mRNA and Inactivated Virus Vaccine and Delivery

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Abstract: The first outbreak of the severe acute respiratory syndrome coronavirus 2, otherwise known as the SARS-CoV- 2, occurred in Wuhan, China in 2019 (COVID-19), and since then it has spread around the world and is a threat to the health of millions of people. Coronavirus is spread similarly to influenza, through airborne particles and starts out in the lungs but then interferes with the immune system which can cause long-term lung damage or death. Currently, there is no public vaccine for people to take, but several companies are working towards developing one to combat COVID-19. This is an especially abnormal case because a pandemic of this scale has never occurred before, as this disease may affect people of all ages, instead of select groups, which is often the case for diseases that people must be vaccinated against. There has been no precedent set for having to immunize every person on the planet, which is why scientists were having difficulties when designing their vaccines, as they had to consider many factors. When the SARS-1 virus happened in 2003 the virus was not very hostile so the vaccine created was not tested on humans, therefore the protective efficiency was not proven. The vaccine created, despite the lack of testing, did allow some researchers to get an idea of where to begin when developing vaccines for SARS-CoV-2. The World Health Organization (WHO) and its partners are working together to track the pandemic, and accelerating the development of a COVID-19 vaccine while maintaining the highest standards on safety.[1] The global effort to speed up the search for safe and effective COVID-19 vaccines is COVAX, which is helping scale vaccine manufacturing capabilities and committing to buy vaccine doses if vaccines are shown to be safe, with the goal of distributing 2 billion doses where they're needed most, worldwide, by the end of 2021. As of November 21, 2020 there are 48 candidate vaccines in clinical evaluation, and 164 candidate vaccines in preclinical evaluation. Of these 48, there have been two primary vaccine platforms that have been successful enough to progress to phase three, which consists of the RNA based platform and inactivated virus vaccine platform. The mRNA vaccine works by giving instructions to our cells to make a spike protein which is found on the surface of a virus that causes COVID-19. This stimulates the cell to display the protein piece on its surface, and the immune system has an immune response against this protein. This would lead to our body being able to protect against future infection by this protein. The inactivated virus vaccine works by using the virus in a weakened or inactivated form. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing. Sinovac Biotech has started to test an inactivated version of SARS-CoV-2 in humans. These two methods both have their advantages and disadvantages, and it is essential to learn about them and the challenges that lay ahead.

Index Terms: mRNA vaccine, spike proteins, coronavirus, distribution

1. Introduction

Coronaviruses are large, enveloped, positive-stranded RNA viruses which contain spike-like projections of glycoproteins on their surface, which appear like a crown under the electron microscope; hence, they are referred to as coronaviruses. The SARS-CoV-2 particles are spherical and have mushroom shaped spike proteins which give it a crown-like appearance. The structural proteins are responsible for host infection, membrane fusion, viral assembly, morphogenesis, and release of virus particles while the nonstructural proteins facilitate viral replication

and transcription. The nucleocapsid protein, membrane protein, envelope protein, and spike protein make up the structural proteins in the coronavirus. [2] The N protein is a part of the viral RNA genome which plays a vital role in its replication and transcription. The M protein is present primarily on the cell surface, and the S-protein is also found on the surface of the virus. This protein is what mediates attachment of the virus to the host cell surface receptors and viral entry into the host cell. The E-protein is a small membrane protein which plays an important role in viral assembly and membrane permeability of the host cell. For the virus to enter and replicate, the coronavirus spike protein attaches to ACE2 receptors found on the surface of many human cells and allows virus entry. The ACE2 protein that SARS-CoV-2 uses as a door to enter cells is also important for regulating blood pressure, which leads to people with high blood pressure with more susceptibility to COVID. Then the spike transforms, unfolding and refolding itself using coiled spring-like parts that start out buried at the core of the spike. Once it hooks onto the cell the virus does membrane fusion which allows the SARS-CoV2 virus to enter and release into the cytoplasm. Proteases uncoat the viral nucleocapsid (N) and then the single stranded RNA is fully released into the cytoplasm. This RNA goes through replication and transcription which generates structural viral proteins, M, S, and E which are synthesized in the cytoplasm. Also in the cytoplasm nucleocapsids are formed and then these self assemble into new virions. These new virions are exported from infected cells through vesicles and spread. Cells from the immune system invade the infected lung tissue to try and remove the virus and clean infected cells, which ends up causing massive amounts of damage. This virus is much more harmful than the normal flu because it has methods to block cells from asking the immune system for assistance. One way that cells try to respond to infection is by making interferon, the alarm signaling protein, but the virus blocks this by a combination of camouflage, snipping off protein markers from the cell asking for assistance, and destroying any antiviral instructions that the cell makes before they can be used. All of this information was discovered after much research and helped scientists come up with vaccines for the future.

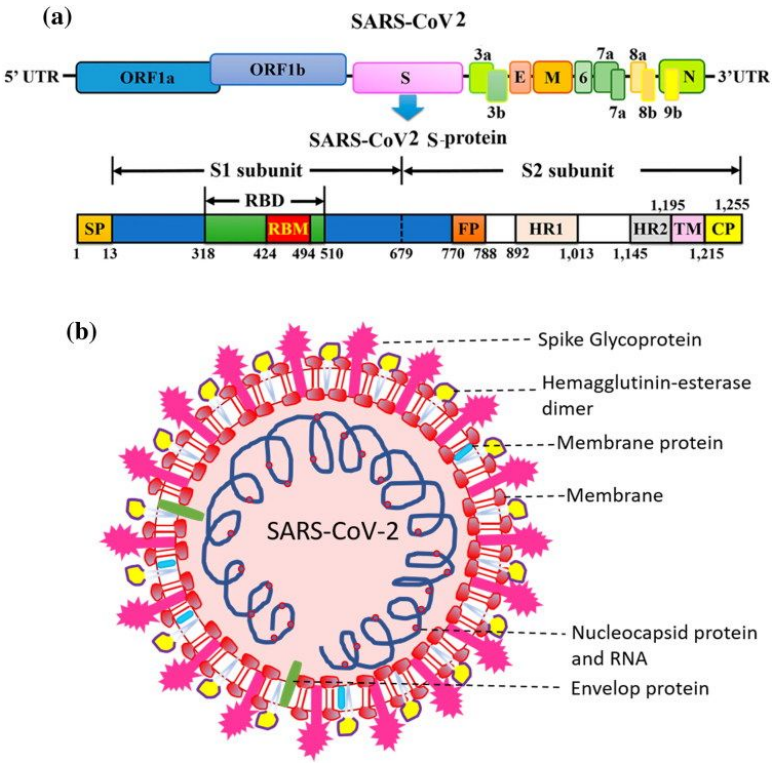

Fig.1 (a) Diagram of SARS-CoV 2 virus structure

2. Methods

2.1. mRNA Vaccine

The first US clinical trial for a vaccine against coronavirus began with the mRNA-1273 vaccine created by Moderna, along with another mRNA vaccine candidate BNT162b2 from BioNTech and Pfizer are both entering phase 3 trials. These vaccines have been created quickly but it is the first time they are being tested in large- scale human trials. The mRNA based vaccines induce activation of the B cells and the cytotoxic T-cells which leads to the destruction of the coronavirus vaccine. The mRNA-1273 is made up of a small piece of mRNA, which is what

carries the instruction of DNA to the ribosome in a form that can code for proteins needed by the body. This mRNA codes for the "spike protein" of SARS-CoV-2 which targets the surface of human cells. The mRNA is coated in oily bubbles made of lipid nanoparticles allowing it to enter the cells easier. Once it enters the mRNA is translated into the spike protein found on the coronavirus and the cell displays the spikes and protein fragments. These protruding spikes and fragments can be recognized by the immune system. Once a vaccinated cell dies the debris will be displayed by an antigen presenting cell, which will lead to the helper T-cell detecting these fragments and call other immune cells to fight the infection. These helper T-cells will be able to find B-cells who have recognized these spike proteins and proliferate to create antibodies. These antibodies now have been created to fit the spike proteins of coronavirus, so the immune system now has a way to detect coronavirus infected cells. [3] Finally, once these antibodies have marked these virus cells, killer T-cells can go and destroy any of the cells that display the spike fragments. It is possible that months after the vaccination, the number of antibodies and killer T-cells will be reduced but this whole process results in memory B-cells and memory T-cells that have retained information on how to detect the spike protein in the future. This vaccine requires 2 injections for the immune system to be well enough equipped to fight off the coronavirus. " A phase 1 clinical trial found the candidate vaccine to be safe, generally well-tolerated and able to induce antibodies with high levels of virus-neutralizing activity. Moderna initiated Phase 2 testing of the vaccine in May 2020. " [5]

2.2 Inactivated Viral Vaccine

The inactivated virus vaccine is a more standard vaccine platform, as it has been used in many other vaccines such as MMR and chickenpox. These vaccines have a weakened version of the live virus to stop it from causing the disease while still leading the immune system to produce memory B and T cells. The company Sinovac created a vaccine candidate called PiCoVacc which induced SARS-COV-2 specific neutralizing antibodies which could neutralize SARS-CoV2 strains. The strain of COVID chosen was CN2 that was then purified and inactivated specific neutralizing antibodies which could neutralize SARS-CoV2 strains.[4] The strain of COVID chosen was CN2 that was then purified and inactivated, with an extra immune booster called alum. [6] There was a phase 1 and 2 trial conducted to further evaluate the safety and immunogenicity of the vaccine and it was found that neutralizing antibodies against the infectious SARS-CoV-2 was detected and there is potential for further investigation. [7]

3. Problems with the Delivery of the Vaccine

In the development of mRNA vaccine, there is the challenge for development, since the vaccine requires freezing temperatures, and is likely to break apart above freezing temperatures. The Pfizer-BioNTech mRNA vaccine "will need to be optimally stored at minus 94 degrees Fahrenheit and will degrade in around five days at normal refrigeration temperatures of slightly above freezing." [8]. These companies are developing shipping containers, but it is unknown how this may affect delivery to third world countries. Some resource-rich countries have already secured large numbers of doses of different candidate vaccines without knowing which one may prove effective and "Given the challenges in resources, manufacturing and issues associated with distribution and regional protectionism, the implementation of vaccination programmes will likely be uneven, asynchronous and variable" [9]. There is much to be decided in the future regarding the distribution of the vaccines, and every drug company is going to have to work hard to ensure their vaccine can be effectively delivered.

4. Conclusion

The COVID-19 virus must be understood fully and the discoveries made about the structure and shape of the virus has allowed for researchers to gain insight on the different methods they may be using to develop an effective vaccine for the population. The mRNA and inactivated virus vaccine are two of the most researched and effective vaccines so far, and it is necessary to continue monitoring their effectiveness as time progresses. While this is occurring, it is essential that research companies and governments work together to ensure a efficient delivery system, so every person in need may be able to receive a vaccine to save their life.

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