An Overview of COVID-19 and Ongoing Development of Vaccines

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ABSTRACT
Coronavirus disease 2019 (abbreviation: COVID-19), is an infectious disease caused by severe acute respiratory syndrome coronavirus type 2 (abbreviation: SARS-CoV-2). The first known patient of the disease was diagnosed in late 2019 in Wuhan, Hubei Province, People's Republic of China, and the disease has since spread globally, resulting in an ongoing epidemic that has become one of the deadliest epidemics in human history. During the study of COVID-19, researchers have combined experiences in the development of SARS-CoV and MERS-CoV vaccines, given that both of them are coronavirus as well, and quickly proposed five major lines of vaccine research: inactivated vaccines, recombinant protein vaccines, viral vector vaccines, nucleic acid vaccines, and live attenuated vaccines. Emerging concepts such as reverse vaccinology and vaccinomics for vaccine design are also on experiments. This article, by means of a view study, provides an overview of the various SARS-CoV-2 vaccines currently in development and clinical trials, and the challenges people would face, such as the increased risk to be re-infected and the potential demand to develop new vaccine, in the present of the new mutant of COVID-19, Omicron.

Keywords：*COVID-19, Pneumonia, Vaccine development, Overview analysis, Omicron.*

1. INTRODUCTION

Coronavirus disease 2019 (COVID-2019), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019 and has spread rapidly across the world due to its high transmissibility and pathogenicity[1]. As of December 25, 2021, more than 279 million confirmed cases and more than 5,395,000 deaths have been reported worldwide [1], and it is still spreading. The World Health Organization (WHO) declared the 2019 coronavirus disease outbreak as a public health emergency of international concern (PHEIC) on January 30, 2020 and assessed on March 11, 2020 that 2019 coronavirus disease has pandemic characteristics. UN Secretary-General Guterres considered the 2019 coronavirus disease epidemic as the most severe crisis facing humanity since World War II[2].

During the COVID-19 study, given that both SARS-CoV and MERS-CoV are also coronaviruses, the researchers quickly came up with five major ideas for vaccine research, taking into account the experience of SARS-CoV and MERS-CoV vaccine development: inactivated vaccines, recombinant protein vaccines, viral vector vaccines, nucleic acid vaccines, and live attenuated vaccines. Emerging concepts such as reverse vaccinology and vaccinomics for vaccine design are also on experiments.

Compared to SARS, COVID-19 presents a lower case fatality rate and higher infectiousness, with mortality rates of approximately 3.7% for COVID-19 and 10% for SARS according to WHO. Besides, COVID-19 quickly develops into different kinds of mutants, further increasing the risk for human to be infected as well as the difficulty to prevent the spread of the pandemic.

In this view, the author summarized the current types of vaccine under development and clinical trials of COVID-19, analyzing the advantages and disadvantages of each strategies. We also discuss the challenges people have to deal with in the present of Omicron, the new mutant of COVID-19 and how to prevent its spread. By analyzing the development of vaccines to help people to know the vaccines better, the study provides widely information about vaccines to the people to some extent.

2. A BRIEF INTRODUCTION OF SARS-COV-2

SARS-CoV-2 belongs to the genus Betacoronavirus Coronavirdae (β-CoV). It is an enveloped linear single-stranded positive-stranded RNA virus with a genome encoding four structural proteins: spike (S), envelope (E), membrane glycoprotein (M), and nucleocapsid protein (N).

The S protein forms a trimeric structure; each monomer can be further cleaved into two subunits S1 and S2. S1 is located at the outermost part of the viral vesicle membrane and is responsible for binding to the cellular receptor angiotensin-converting enzyme 2 (ACE2); S2 is located close to the viral vesicle membrane and is responsible for inducing the fusion process between the virus and the cell membrane. S1 mainly includes 2 parts, N-terminal structural domain (NTD) and C-terminal structural domain (CTD), where S1 binds directly to ACE2 receptor, so it is also called receptor binding domain (RBD). S2 mainly contains fusion peptide and 2 heptapeptide repeat domains (HR1, HR2). [3]

Due to its high sequence similarity among different coronavirus, S2 is a potential target for broad-spectrum anti-coronavirus drugs.

3. IMMUNE DESIGN STRATEGY FOR THE VACCINE

3.1. S protein

S protein is able to stimulate the body to produce a high intensity humoral and cellular immune response. It is currently the most important immunogen in the development of new crown vaccines. Following the COVID-19 outbreak, several global teams around the world have successfully screened the blood of infected/recovered individuals for multiple strains of human antibodies with extremely high neutralization activity. In addition, S proteins are also the main target of T cell response. It has been demonstrated that SARS-CoV-2 infection stimulates the production of S protein-specific CD4+ and CD8+ T cells, indicating that S proteins can activate cellular immunity[4].

S proteins in their natural state are not stable during in vitro expression and often spontaneously change from the prefusion conformation to the postfusion conformation, which seriously affects the immunogenicity of the vaccine. To enhance the stability of the prefusion conformation of S proteins, researchers commonly mutate K986 and V987 of SARS-CoV-2 S protein to proline (P) respectively to form a structurally stable prefusion conformation (S-2P) protein by using point mutations[5]. Researches also found that the stability of the S protein can be further enhanced by mutating or deleting the multi-base enzyme excision site (RRAR) between S1/S2 in SARS-CoV-2[6]. In addition, it has been found that fusion expression of a human-derived trimer-tag with S proteins is able to form a disulfide-linked homotrimeric protein in the prefusion conformation, which is able to mimic the natural structure of S proteins on the surface of viral particles and stimulate the production of high-school and active antibodies[7]. All of the modification strategies have been applied to the development of novel COV vaccines.

3.2. RBD

RBD is a domain where S1 binds directly to ACE2 receptor. It was found that immunization with RBD alone not only resulted in a large number of high and viable antibodies, but also has the potential to avoid potential side effects such as antibody dependent enhancement (ADE). In addition, it was found that RBD contains both T-cell-reactive antigenic epitopes, suggesting that immunization with RBD can activate both humoral and cellular immunity. In order to further improve the immunogenicity of RBD, the current optimization strategies include tandem expression of the Fc structural domain, simultaneous expression of multiple RBD monomers on the same vector multiple RBD monomers on the same vector, or multimerization modification of the RBD, etc.

4. MAJOR TYPES OF COV VACCINES AND RESEARCH PROGRESS

4.1. Inactivated vaccines

Inactivated vaccines is a vaccine in which a highly immunogenic pathogen is artificially cultured in large quantities and then inactivated by physical (UV) or chemical (methylal/β-propanolactone) methods so that it loses its pathogenicity but the immunogenicity is retained. This type of vaccine is the most classic vaccine development pathway, with It has the advantages of mature technology, quality control and clear evaluation index.

4.2. Viral vector vaccines

Viral vector vaccines are vaccine types that use viral vectors with or without the ability to replicate to deliver immunogens. As of January 2021, WHO statistics show that there are 17 such vaccines in clinical trials of which the replication-competent viral vectors are relatively diverse (6 in total), while the non-replicating viral vectors are more concentrated (11 in total), mainly adenovirus (8), and mumps virus (1). The viral vectors with no replication capacity were concentrated (11 in total), mainly adenoviruses (8), while mumps virus (1) and modified pox virus (2) could also be used as vaccine vectors[8]. There are three main types of adenovirus vectors used in the development of the new crown

vaccine, namely Ad5 and Ad26 of human origin and ChAdOx1 of chimpanzee origin.

4.3. Nucleic acid vaccines

DNA vaccines and RNA vaccines are collectively known as nucleic acid vaccines, which is an emerging technology for vaccine development in recent years. This type of vaccine is direct introduction of DNA or RNA fragments into host cells and

directly into the host cell and then express the target protein and stimulate specific immunity. Compared with traditional vaccine development technologies, DNA and DNA vaccines can be made quickly because they require no culture or fermentation, instead using synthetic processes. Developers' and regulators' experience with these platforms for personal oncology vaccines can facilitate rapid testing and release. There are no approved RNA vaccines to date, but RNA vaccines have entered clinical trials, and regulators have experience in reviewing clinical trial applications and with associated manufacturing of the vaccines[9].

However, there are potential risks of integration into the organism's own genome and disadvantages such as easy degradation and harsh storage and transportation conditions.

Compared to DNA vaccines, the development of RNA vaccines is progressing more rapidly. Seven RNA vaccines have now entered clinical trials worldwide, with three three of them are in Phase III clinical trials, while there are currently eight DNA vaccines in clinical trials.

The safety of mRNA vaccines and and persistence of immunity remain a major concern. The mRNA vaccine (ARCoV) jointly developed by Watson Biologicals and the Academy of Military Medical Sciences is currently in Phase I clinical trials.

The vaccine can be stably stored and transported at 4 ℃, which overcomes the problem of BNT-162 and mRAN-1273 that must be stored and transported at -80 ℃, which is conducive to future large-scale use of the vaccine[10].

4.4. Subunit vaccines

Subunit vaccine is a viral antigen target gene on an expression vector and induced by in vitro expression system to express the antigenic protein on an in vitro expression system and using it as an immunogen. The immunogens used in the SARS-COV-2 subunit vaccines are mainly modified recombinant S proteins or RBD proteins.

4.5. Live attenuated vaccines

Live attenuated vaccines are direct immunizations against live viruses that lose their pathogenicity but retain their immunogenicity, thus stimulating the body to produce a strong immune response. Live attenuated vaccines include live attenuated polio vaccine, live attenuated encephalitis B vaccine, etc. At present, there is only one live attenuated vaccine for the COVID-19 in the world, which was jointly developed by the United States and India.

5. CHALLENGES IN THE CONTEXT OF OMICRON EPIDEMIC

Despite the unprecedented pace of development of the neo-crown vaccine, the diverse types of development, and the Phase III clinical data of several vaccines showing effectiveness well beyond expectations, the efficacy, safety, and durability of the neo-crown vaccine are still being tested as SARS-CoV-2 continues to spread and mutate globally. A study using a pseudovirus model found that different point mutations on the S protein significantly affect the protective effect of neutralizing antibodies, suggesting that the continuous mutation of SARS-CoV-2 does affect the effectiveness of the COVID vaccine.

Recently, the World Health Organization issued a statement, listing the new coronavirus variant B.1.1.529 as the fifth "variant of concern" (VOC) with Greek letters Omicron. The statement mentions that preliminary studies have shown that, compared to other variant of concern strains, the variant causes an increased risk of re-infection in humans compared to other strains of concern. It has a large number of mutations, several of which may have an impact on its transmission ability and degree of pathogenicity.

As of November 28, 2021, the importation of the mutant strain has been monitored in South Africa, Israel, Belgium, Italy, the United Kingdom, Austria, and Hong Kong, China. Although the actual impact of the mutant strain on existing vaccines is not yet known, several vaccine manufacturers in China and abroad have stated that they are collecting and analyzing relevant information to determine whether the strain will weaken the protective effect of the vaccine and have started to develop vaccine candidates against the new mutant strain. Its strong ability to escape from the human immune system makes it a new challenge in the Outbreak Prevention and Control of SARS-COV-2[11].

6. CONCLUSION

In the present scenario, the development of a new therapeutic agent for COVID-19 is not a feasible option with regard to available time. So, the experiments on enforcing strict preventive and control measures that minimize the risk of possible disease transmission become increasingly important.

The vaccine still has an enormous and irreplaceable role to play in containing the ongoing COVID-19 pandemic worldwide. Although the continuous mutation of SARS-CoV-2 does affect the effectiveness of the COVID vaccine, as the understanding of SARS-CoV-2 continues to and continuous breakthroughs in vaccine development technology, the epidemic of SARS-COV-2 would eventually be resolved in the future, and one of the most effective way is to increase the vaccination rates and thus lead to herd immunity.

For the new mutant Omicron,the author believes, if the prevention and control strategies implemented are effective, it is unlikely to become the dominant strain worldwide even. The world can prevent the epidemic of Omicron as long as they adhere to regular control measures, steadily promoting people to get vaccinated, just like dealing with other mutants in the past. In this way, the spread of Omicron would be limited, too.

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