International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 5 Issue 2, January-February 2021 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Prospects and Problems of Development of Candidate Vaccine against COVID-19

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ABSTRACT

There is an urgent need to develop a vaccine against coronavirus disease 2019 (COVID-19), which is caused by a new coronavirus, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Although vaccine development typically requires 3 to 5 years, there is a possibility that the vaccine developed for either severe acute respiratory syndrome (SARS) or the middle east respiratory syndrome (MERS) could be used against COVID-19 as well. Therefore, a vaccine against COVID-19 is expected to be commercialized within 1 to 2 years. If so, it will be the fastest vaccine development in human history.In this review, we have summarized the information released as of April 10, 2020.

KEYWORDS: *Vaccine, COVID-19, SARS-CoV-2*

How to cite this paper: Takuma Hayashi | Yasuaki Amano | Takashi Ura | Ikuo Konishi "Prospects and Problems of Development of Candidate Vaccine against COVID-19" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-5 | Issue-2, February 2021, pp.604-606, URL: www.ijtsrd.com/papers/ijtsrd38521.pdf

IJTSRD38521

The Principle behind Vaccine Development is Pre-learning of Immunity: Vaccine Development is Accelerated by Biotech

The basic principle of a vaccine is to allow the immune system to learn and remember aspects of specific pathogens (virus or bacterium) in advance. This prepare the body to generate a rapid immune response when a real pathogen invades the body, reducing the severity of pathological conditions caused by the pathogen. Currently, clinically used vaccines are manufactured by culturing and propagating a real pathogen with great care, then attenuating and inactivating it. However, with developments in biotechnology, easier and faster vaccine development is now possible.

There are 4Major Platforms for Vaccine Development

The vaccine platforms currently under development are: (1) messenger ribonucleic acid(mRNA) vaccine, deoxyribonucleic acid(DNA) vaccine, (2) attenuated vaccine and an inactivated vaccine that attenuates SARS-CoV-2 for use as a live vaccine, (3) recombinant protein vaccines, and (4) vector vaccines.

I. mRNA and DNA Vaccines

mRNA vaccine refers to the inoculation of mRNA of spike glycoprotein existing on the surface of the SARS-CoV-2 virus into the body, prompting spurious glycoprotein to be produced in the body's cells. This is the mechanism by which the immune response is strongly induced in the body.

Spike glycoprotein is a structural protein used when a virus invades cells of the living body and is a target of attack by immune cells. Once the in vivo presence of pseudo spike glycoproteins is detected by the body, the immune system learns the antigen-antibody response to SARS-CoV-2.As a result, a genuine immune response to SARS-CoV-2 is promptly induced, and infection and aggravation of pathological conditions are suppressed.

Unlike the conventional vaccine production process, if researchers can decipher the genome information of the virus, they can chemically synthesize the mRNA encoding the pseudo spike glycoprotein based on this information. Large quantities of mRNA vaccines can be manufactured. In addition, even if the SARS-CoV-2 mutates, researchers only need to change the blueprint of the mRNA, which allows a flexible and rapid response to SARS-CoV-2.

mRNA-1273, an mRNA vaccine jointly developed by Modelna Inc. and the National Institute of Allergy and Infectious Diseases, is currently at the forefront of race to develop a vaccine. On March 16, 2020, the first phase I clinical trial for a SARS0CoV-2 vaccine in the world was started. The trial includes 45 healthy men and women between the ages of 18 and 55 years. The mRNA vaccine will be administered twice at 4-week intervals to confirm and evaluate the safety of mRNA and the acquisition of immunity.

At the end of December 2019, a "pneumonia never seen" was reported in China. A few weeks later, a Chinese research team deciphered and published the virus' genomic information, including spike glycoproteins. As a result, the new coronavirus was determined to be a SARS-related virus, and the race to develop a vaccine began. Modelna Inc., a company with experience developing a vaccine for SARS and MERS, narrowed down the vaccine candidates in just 1.5 months based on the genome analysis of the virus and started a phase I clinical trial in humans. According to the best and shortest scenario, this mRNA vaccine may have clinical application in approximately 1.5 years.

The challenge is that the mRNA vaccine's immunostimulatory capacity is not very high. For this reason, an immunostimulant known as an adjuvant must be added to the mRNA vaccine. It is still unclear whether the adjuvants used in traditional vaccines or the newly developed adjuvants for mRNA will be effective because the immune response observed in animal experiments cannot always be detected in humans. First, researchers should review the results of the phase I trials. If they see promise, they should then further confirm the efficacy of the vaccine in phase II and III trials in larger populations. In these studies, problems such as vaccine safety and unexpected side effects may arise.

Regarding mRNA vaccines, in addition to Modelna, Biontec Co., Ltd. in Germany has announced that it will jointly develop an mRNA vaccine, BNT162, with Pfizer Inc. for global distribution. In Japan, the Institute of Medical Science, University of Tokyo, is co developing an mRNA vaccine with a major pharmaceutical company, but that study is still in the animal experiment stage.

Regarding the development of DNA vaccines, Anges Co., Ltd. is cooperating with Osaka University to produce a plasmid DNA vaccine into which a gene encoding a spike glycoprotein of SARS-CoV-2 has been introduced. When this DNA vaccine is inoculated, a pseudo spike glycoprotein is produced in the body and an immune response is induced.

Unlike mRNA vaccines produced by chemical synthesis, recombinant DNA is produced and purified using Escherichia coli as a host to produce a stock solution of the vaccine, which is expected to shorten the production period. Takara Bio Co., Ltd. is cooperating in the production of DNA vaccines. Animal testing advanced in March 2020, and clinical trials in humans are scheduled to begin in the fall. Also, on April 6, 2020, it was reported that Inovio Inc. in the United States started clinical trials for DNA vaccines for humans. In this clinical study, 40 healthy adults will be vaccinated twice at 4-week intervals to confirm the safety and efficacy.

II. Inactivated and Attenuated Vaccine

Attenuated vaccines, such as the measles vaccine, are viruses and bacteria that have extremely weakened virulence used as vaccines. After immunity is obtained, there is an advantage that the immune effect against the antigen is strong and that the immune memory can last for a long time. The disadvantage of this type of vaccine is that the pathogen can regain toxicity and develop disease. In addition, strict control is required in order to prevent contamination with other microorganisms in the manufacturing process. In this way, there are many hurdles to be cleared in the manufacturing process of DNA vaccines.

Viruses and bacteria that have been cultivated in large quantities are purified and treated with chemicals to eliminate toxicity before being used as inactivated vaccines. Inactivated vaccines do not grow in vivo like live vaccines, so multiple inoculations are required because a single inoculation does not achieve or maintain a sufficient immune effect against the antigen. Although biotechnology is evolving, time and large-scale equipment are required to attenuate the virus. For individuals who feel that the speed of development of inactivated vaccines is too slow, an inactivated vaccine that can achieve a high immune effect may be a favorite. In February 2020, vaccine manufacturers in the United States and India jointly announced the development of an attenuated vaccine. In addition, vaccine development is underway at several universities, research institutes, and bioventure companies that have developed SARS inactivated vaccines.

III. Gene Recombinant Protein Vaccine

In the biotechnology era, new vaccine candidates such as mRNA vaccines are peptide vaccines produced using genetic engineering technology. Viral antigenic proteins and some peptides produced and purified by plant, insect, and animal cells are clinically applied as vaccines. On February 18, 2020, the French company Sanofi, which has experience developing a SARS vaccine, announced that they will jointly develop a new COVID-19 vaccine using genetic modification technology with the United States Agency for Advanced Biomedical Research. In addition, Johnson & Johnson in the United States is developing genetically engineered protein vaccines using proprietary technology.

IV. Vector Vaccine

One of the key points in vaccine development is the in vivo expression method of the pseudo spike glycoprotein as an antigen, which is a target of attack for immune cells. There is a simple method of inoculating an attenuated strain, a method of inoculating a "blueprint" of the mRNA or DNA to replicate in a living cell, and a method of inoculating a detoxified virus as a vector in vivo. The backbone of the viral vector used is composed of genes such as an adenovirus or measles virus that cause common colds. Currently, Sanofi, Johnson & Johnson, Inc., and several bioventure companies are preparing to manufacture vector vaccines. In addition, Japan's ID Pharma Co., Ltd., which has experience developing tuberculosis vaccines, is jointly developing a vector vaccine based on the Sendai virus gene with the Shanghai Guangzhou Sanitary Clinical Center, Fudan University, in China.

V. Does BCG Prevent COVID-19?

Over the past few weeks, information has spread, centering on the strategic national stockpile, questioning whether the Bacille Calmette-Guérin (BCG) vaccine be effective in preventing COVID-19 infection. The origin of this information was a study published in 2011, which demonstrated that BCG vaccination programs and vaccine strains vary from country to country [1]. This study was a reference for developing a better vaccination program. However, the classification of BCG regular vaccination countries and non-vaccination countries published in this document exploded with countries where COVID-19 outbreaks were relatively moderate (eg, Japan, South Korea, and Eastern countries)or countries that have been affected by the epidemic (eg, European countries and the United States). It has been reported that COVID-19 mortality rates are low in countries that routinely inoculated Japanese and Russian strains of BCG [2].

BCG is a vaccine that aims to prevent bacterial infections known as Mycobacterium tuberculosis. In other words, BCG has no effect in preventing viral infections and cannot directly counter a SARS-CoV-2 infection. At this time, there is a solid hypothesis that BCG vaccination might strengthen the entire immune system, but there is no conclusive evidence.

However, because there is evidence that cannot be ignored in this study, several countries, including the Netherlands and Australia, have started prospective clinical trials of BCG vaccination in healthcare workers who are at high risk of infection. If a slight effect can be confirmed, BCG vaccination may serve as a bridge until a formal vaccine is established. In addition, since 1951, regular vaccinations have been given to infants, children, and students in Japan. Because of this, there may be fewer COVID-19 deaths.

On April 4, 2020, the Vaccine Society of Japan officially stated that the protective effect of BCG against SARS-CoV-2 infection has not been scientifically proven at this time and announced that BCG vaccination against COVID-19 is not recommended. Recent clinical study does not support the idea that BCG vaccination in childhood has a protective effect againstCOVID-19 in adulthood [3].At this time, the recommendation best determined to have a preventive effect is that people avoid contact with others in closed, dense spaces. Furthermore, it is important for people to wash their hands and disinfect their hands after touching equipment and tableware touched by an unspecified number of people. People should avoid unnecessary and rushed outings. It is important for people to stay home to save themselves, their families, and others.

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On April 24, 2020, the World Health Organization (WHO)indicated that there was no scientific basis for preventing infected persons who recovered after being infected with the new coronavirus from receiving a second infection. When an individual is infected with a virus, antibodies remain present in the body, making it difficult for that induvial to be re-infected with the same virus. The WHO indicated that an individual could prevent reinfection if infected with the new virus and enough antibodies were made in the body. However, the WHO pointed out that there are cases in which the amount of antibody produced is exceptionally low.

Therefore, there is no scientific basis that people will not become re-infected if they carry the antibody. In addition, some countries are considering issuing a so-called immunity certificate that will allow people who have been confirmed to have antibodies to return to work. The WHO warned that such systems could increase the risk of infection.

Unprecedented scale of resources has been invested in the development of the COVID-19 vaccine, as such, this is likely to have future benefits. Outbreaks of SARS in the early 2000s were virtually eradicated by preventing infections, resulting in no need for vaccines. But for pandemic COVID-19, there is a need for vaccines around the world. The WHO emphasizes that COVID-19 vaccines and treatments must be available to all people, regardless of country. In April 2020, WHO announced the Access to COVID-19 Tools (ACT) Accelerator as an international initiative to accelerate the development, production, and fair distribution of COVID-19 vaccines, diagnostics, and treatments.

Footnote

On May 18, 2020, an American biotechnology company "Modelna" developing a novel coronavirus vaccine announced that antibodies were confirmed in all participants in an early stage clinical trial targeting a small number of people. No major side effects were observed in this clinical trial. From July 2020, Modelna will begin phase III clinical trials in the thousand participants. A spokeswoman for the local media said Modelna executives could potentially commercialize the vaccine as early as early 2021.

Disclosure

The authors declare no potential conflicts of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We thank Professor Richard A. Young (Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA) for his research assistance. This study was supported in part by grants from the Japan Ministry of Education, Culture, Science and Technology (No. 24592510, No. 15K1079, and No. 19K09840), the Foundation of Osaka Cancer Research, The Ichiro Kanehara Foundation for the Promotion of Medical Science and Medical Care, the Foundation for Promotion of Cancer Research, the Kanzawa Medical Research Foundation, The Shinshu Medical Foundation, and the Takeda Foundation for Medical Science.

References

[1] Zwerling A, Behr MA, Verma A, et al. The BCG world atlas: a database of global BCG vaccination policies and practices. PLoS One 2011;8:e1001012.

[2] Miller A, Reandelar MJ, Fasciglione K, et al. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiolgocal study. medRxiv 2020 Mar 24. doi:10.1101/2020.03.24.20042937.

[3] Hamiel U, Kozer E, Youngster I. SARS-CoV-2Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA. 2020 May 13. doi: 10.1001/jama.2020.8189.