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Immunological Rationale for Developing an Effective Vaccine for COVID-19

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Abstract: *The recently developed coronavirus (SARS-CoV-2) and the disease it causes – COVID-19 – has altered the world we know. The research of COVID-19 is now focused on acquiring new evidence on immunology, including immune memory against the virus, developing new tools for infection identification and effective vaccines. However, the lack of unconditional data exceeds the proven information of the SARS-CoV-2 and COVID-19.Both humoral and cellular immunityare implicated in the disease's pathophysiology. Cell-mediated immunity is the leading and efficient immune response to viral infection. As far as the clinical image of COVID-19 is concerned, it remains uncertain and volatile, as well as immune memory and the risk ofreinfection. There are, also expectations for the developmentof a successful vaccine against the virus.Direct SARS-CoV-2 vaccines' development continues to be complicated, because there are several forms or subtypes of coronavirus. Edward Jenner's solution should also be considered, or just a the production of a vaccine against the entire family of coronaviruses or against those that cause disease in animals only.*

Keywords: *SARS-CoV-2, COVID-19, immune memory, anti-SARS-CoV-2 antibodies, COVID-19 vaccine, vaccine development.*

1. Introduction

The research of COVID-19 is now focused onacquiring new evidence on immunology, including immune memory against the virus, developing new tools for infection identification and effective vaccines. However, the lack of unconditional data exceeds the proven information of the SARS-CoV-2 and COVID-19.

The problem with the immune memory for COVID-19 is on the rise. The main question is whether there is long immune memory against the virus.Can we be sure that possession of SARS-CoV-2 antibodies would prevent fromre-infecting again? Or, whether antibodies acquired after vaccination would protect us from getting the virus?Is it possible for people with anti-SARS-CoV-2 to feel safe and to shed the infection more easily? False-positive and negative findings also pour oil on the fire.

It is currentlychallenging to say that convalescent peoplewould be protected from infection if they have~~a~~ certain amount of antibodies in their blood. Any forecasts based on the antibody existence have legal and ethical consequences. Such a false sense of security may also promote risky behavior, such as refusingto wearrefusal of wearingmasks and maintaining social distances. Besides, there would be people who would deliberately attempt to get sick to obtain antibodies. For some of them, the infection would be fatal.

2. SARS-CoV-2 Vs. Immune System

It is well-known that cell-mediated immunity is primary for fightingagainstviral infections. Not surprisingly, recent resultsconclude that even in decreased numbers, T lymphocytes, both helper and cytotoxic, are overactivated in patients infected with SARS-CoV-2[1]. This significant decrease in numbers of immune cellsis

primarilyseeninthe acute phase of COVID-19 patients.

However, once differentiated in the organism, CD4 + and CD8 + anti-virus memory T cells survive in the bloodstream of recovering patients for up to four years, even in the absence of viral antigens[2]. Other studies have also found SARS-CoV-S protein-specific memory T cells in patients four years after the infection [3] and MERS-CoV-specific CD8+ T cells in mice, primarily involved in viral clearance[4]. These results provide a fair framework for the design of successful SARS-CoV-2 vaccines.

One of the prominent immunological features of COVID-19 is the exhaustion of lymphocytes. Among other immunological properties of COVID-19 are the decreased functional diversity of immune cells linked to a severe course of the disease[5,6].The decreased functional diversity of immune cells is another immunological propertiy of COVID-19 and it is linked to a severe course of the disease.The compromised immune response makes the development of adequate immune memory quite doubtful.However, recovering patients had some SARS-CoV-specific antibodies up to 2-6 years after infection, unless they haddevelopedacute respiratory distress syndrome (ARDS), which contributed to undetectable peripheral memory B cell reactions [3,7]. It is not clear if the T cell response is adequate to protect from reinfection[8]. To develop its defensive immune response during the incubation phase and mild to moderate disease, the host must be in good general health and specific genetic terrain. For example, some HLA antigens would help develop a specific anti-viral immunity. Also, genetic variations are believed to lead to human differences in the immune response to pathogens.

However, all of the mentioned above, is extremely important for the developing a vaccination policy since an efficient and safe vaccine is desperately reliant on the probability of possessing immune memory after a virus has occurred[8].

Typically, survivors of COVID-19 developed antibodies 2-15 days after symptoms had occurred. The immune response is generally reminiscent of normal anti-viral reactions[9]. The majority of patients developed antibodies against spike proteins[10]. Besides, antibody levels are associated with the age of the patients` age and the severity of the clinical course of the disease. Antibody levels werefound to be higher in the elderlyones and those who had a more severe infection. Women had lower levels of antibodies than men, and smokers had lower levels than non-smokers.

An Icelandic study shows that new, different antibodies against the virus appear a few months after the diagnosis. They are probably more durable and effective [11].The second wave of antibodies is likely to be produced by a smaller number of longer-lived plasma cells that provide long-lasting immunity.

However, more testing for antibodies against the coronavirus is needed. A disadvantage of the antibodies testing is that there were no detectable antibodies in some people, probably such had not formed in mild disease. Immune responses vary considerably from individual to individual. It is not yet clear whether antibodies can prevent recurrence and provide long-term immunity.Some in vitro studies with anti-SARS-CoV-2 antibodies have shown that they can neutralize and block the virus from penetrating the host cells[12].

In all cases, we have to bear in mind that cellular immunity to the virus is more critical for viral clearance than a humoral response. Thus, the function of T-helper, T-cytotoxic, and NK cells should not be ignored. Studies involving survivors of the 2003 SARS outbreak have recently shown that neutralizing antibodies have been detected 17 years after the infection[13]. Similar findings had been reported for the MERS virus. However, the amount of neutralizing antibodies has decreased dramatically after three years.

In comparison, it has been shown that people exposed to the virus for the second time have had a much milder disease, even though reinfection may occur[14]. The explanation for the decrease in antibody levels remains unclear. Some explanations were related to the short-lived memory B cells, particularly against coronavirus, which stay hidden in secondary lymphoid organs (i.e., lymph nodes, spleen), as well as in the bone marrow and lungs. Interestingly, except for antibody amounts, memory B cells may also be isolated and investigated as a piece ofevidence for a prior virus experience. In addition, some of the memory B cells in some patients responded to live virus proteins in vitro[15].

The most importantaspect of the unknown immune response and immune memory of SARS-CoV-2 infection is the world's desire to

invent an efficient vaccine against the virus. This vaccine is essential to minimize the disease's seriousness, clear the virus, and spread it while monitoring existing and potential coronavirus outbreaks. There are several methods for the development of SARS-CoV and MERS-CoV vaccines studied in animals. This includes the use of live attenuated viruses, viral vectors, inactivated viruses, vaccine subunits, recombinant DNA, and protein vaccines[15]. There may potentially be other attractive targets for use in the formulation of SARS-CoV-2 infection and therapy vaccines, but further laboratory and clinical data are also required. Several trials are underway, but the production of SARS-CoV-2 vaccines still takes months to years.

Since antibodies to COVID-19 can be found in the blood of those who have had recovered from the disease, according to the latest studies, we have hope. And it is also encouraging for the effectiveness of the vaccines that are being currently tested. However, another study shows that COVID-19 can be caught repeatedly.

Unfortunately, the host's immunity to this unpredictable and highly contagious virus may be transient. It may be similar to that caused by most other common viral infections.

3. Vaccines Against SARS-Cov-2

More than 170 countries have already joined the COVID-19 Vaccine Global Access Facility or COVAX - the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator, as the WHO announced recently [16]. The collaboration aims to accelerate the development of vaccines, produce doses for all countries, and distribute them, especially to people at the highest risk of COVID-19 infection and complications. In fact, the process of developing vaccines requires a global network for the supply, production, and distribution of doses to humans, including vaccine components such as syringes and vials.

To help accelerate the trials' development and funding, the United States created Operation Warp Speed in partnership with the Department of Health and Human Services, the FDA, and other federal agencies. Its goal is to deliver 300 million doses of a safe, effective vaccine by January 2021. The program includes such companies as AstraZeneca, Janssen (Johnson & Johnson), Moderna, Novavax, Pfizer, and Sanofi / GSK.

Nearly 200 vaccines for the disease are under study, and several candidates have moved on to phase III human clinical trials. This is the last step in proving whether a vaccine is safe and effective before the FDA approves it.

For a vaccine to be approved by the FDA, it will need to prevent infection or reduce its severity in at least 50% of vaccinated people. As with any vaccination, the goal is to immunize many people with a vaccine so that the established immunity that covers the community. Thus, even the unvaccinated will be protected by herd immunity. Some experts believe that about 60% to 70% of the population should develop antibodies for the current coronavirus pandemic, whether through a vaccine or recovery from COVID-19. History has shown that only through vaccination, not through disease, such a disease can be eradicated.

In other words, if not enough people are vaccinated, and only the disease is relied on, herd immunity may not develop. However, it is equally vital for vaccine manufacturers to prove that they are safe. The FDA also said it could issue an emergency authorization for a vaccine against COVID-19, but this would be decided on a case-by-case basis.

Phase III trials confirm and extend the safety and efficacy results of earlier trials of the vaccines.

One of the vaccines was made with a weakened version of the common cold virus, an adenovirus taken from chimpanzees where the adenovirus is genetically modified not to reproduce. The vaccine combines with the SARS-CoV-2 spike protein genes to cause the production of antibodies against it, which allows the immune system to kill the virus. This vaccine also stimulates T lymphocytes from a single dose leading to a 4-fold increase in antibodies in 95% of participants one month after vaccination. While one dose was sufficient to maintain T-cell immunity for at least two months, two doses were most effective. No severeadverse effects have been reported.

Other vaccines used messenger RNA (mRNA) in different combinations to different antigens to produce antibodies. Early results from an ongoing phase I / II study of the vaccine showed that it "elicits a strong immune response" in all adults tested who received it. The average and highest doses elicited approximately the same immune response. Side effects were usually mild to moderate, including fatigue, headache,

fever, sleep problems, and pain at the injection site.

The virus-making protein of the virus is a crucial protein on the surface that allows it to enter cells when a person becomes infected. Once injected, the mRNA from the vaccine instructs the cells to make copies of the spike protein, acting as if they were infected with the coronavirus.

Other vaccines that use an inactivated version of the virus showed a strong neutralizing immune response with antibodies production in 97.6%-100% of individualsafter 14 days, depending on the time and dosage of injections, without serious adverse effects.

The technology uses DNA and itis designed to produce a specific immune response. A smart device uses a short electrical impulse to open small pores in the skin and apply the vaccine. Once the DNA enters the cell, it instructs it to make many copies of it and to stimulate an immune response in the body.Encouraging results from the early phase I were announced, finding that 94% of the 40 phase I volunteers had an immune response at week six after two doses of the vaccine.

Some vaccines combine coronavirus genes with a modified adenovirus and a technology that generates antigens (which stimulate the immune system) derived from the coronavirus protein. Two different doses were being tested, including an adjuvant designed to boost the immune response, all of which well-tolerated and inducing antibody production in healthy adults tested. The most common side effects were malaise and pain. All volunteers developed antibodies after a single dose and all developed neutralizing antibodies after the second dose.

4. Conclusion

In summary, it is troubling that some patients remain positive for the infection following discharge from hospital, while others recover with a relapse. This indicates that the immune reaction to SARS-CoV-2 produced to neutralize and remove the virus could be ineffective in some patients. Also, this finding will suggest that vaccination may not be efficient in these individuals. Patients who have not reached a critical stage of the illness should be checked for the existence of the virus and the assessment of the T / B cell response. Any of these scenarios must be considered when defining vaccine production techniques. In addition, due to several forms or subtypes of coronavirus, direct SARS-CoV-2 vaccines' development continues to be complicated. Edward Jenner's solution should also be considered, development of a vaccine against the entire family of coronaviruses or against those that cause disease in animals only.

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