A brief outlook on the current emerging trends of COVID 19 vaccines

INTRODUCTION

COVID-19 has cruised to our lives undoubtedly and is still heading its frontline claiming itself as the worst pandemic of this century. As human history had witnessed more drastic events in the past, evolving through each of them has always brought about a better scientific temper and understanding. The clues of the pandemics from its initial trials to its outrageous transmission process are continuously evolving, and the utmost need of the era undoubtedly will be a successful vaccine to eradicate this pandemic threat at the earliest.

Time since the Vedic period, the importance of immunity and various primitive methods of immunization were explored, which eventually had evolved itself, into a vaccination regimen against major infectious diseases.[1] The concept of immunization was introduced and scientifically implemented by Edward Jenner. He is considered as the founder of vaccinology in the West in 1796, after he inoculated a 13-year-old-boy with vaccinia virus (cowpox), and demonstrated immunity to smallpox. In 1798, the first smallpox vaccine was developed. Over the 18th and 19th centuries, systematic implementation of mass smallpox immunization culminated in its global eradication in 1979. The past two decades have seen the application of molecular genetics and its increased insights into immunology, microbiology and genomics applied to vaccinology.[2]

Molecular genetics has set the scene for a bright future for vaccinology, including the development of new vaccine delivery systems (e.g., DNA vaccines, viral vectors, plant vaccines and topical formulations), new adjuvants and few other therapeutic vaccines, which are currently available. Influenza vaccine was the first successful inactivated virus vaccine,[3] and experience with that vaccine served Salk well in his successful effort to develop an inactivated polio vaccine.[4] Later, hepatitis A vaccine was prepared by Provost *et al.*, also based on chemical inactivation.[5] The excellent efficacy of the latter testifies to the ability of careful inactivation to maintain immunogenicity. Whole inactivated viruses or subunits of virus have been used to make successful vaccines against Japanese encephalitis virus and tick-borne encephalitis virus.[6-8] Chronology of the major viral vaccines hints that the development of these took a considerable amount of time from inception to its final delivery.

Focus on developing a vaccine against the current global pandemic is a bit challenging and demanding for researchers. As the efforts are only aspiring for a pandemic free world, it is important to discuss various immunological mechanisms associated with the major promising vaccine and their targeted approach.

HOW DIFFERENT IS SARS-COV 2?

Looking back to the smaller pandemics' outbreaks of SARS-CoV in 2003 and MERS in 2012 (Saudi Arabia), only two vaccine candidates and one mAb panel have entered Phase I clinical trials for safety. Ironically, no vaccines and treatment strategies have been approved for SARS-CoV infection even after more than a decade of outbreak history.[9] The delayed translation of these diseases into vaccine development has had an impact in rediscovering the vaccination strategy for SARS-CoV 2 or COVID-19.

When compared to SARS-CoV and MERS CoV, SARS-CoV 2 has got a similar structure covered with pointed structures that surround them like a corona or crown due to the presence of spike glycoproteins on their envelope[10] [Figure 1]. The life cycle of SARS-CoV-2 in human lung cells is commonly noted. Coronavirus is most often transmitted by droplets while sneezing and coughing, and its journey begins on the 1st day after infiltration from the upper respiratory tract. The spike proteins of SARS-CoV-2 bind to angiotensin-converting enzyme 2 (ACE2) receptors. The virion then releases RNA genome into the cell, and the translation of structural and nonstructural proteins follows. ORF1a and ORF1ab are translated to produce pp1a and pp1ab polyproteins, which are cleaved by the proteases that are encoded by ORF1a to yield nonstructural proteins. This is followed by assembly and budding into the lumen

of the Endoplasmic Reticulum–Golgi Intermediate Compartment. Virions are then released from the infected cell through exocytosis.[11]

The development of vaccine is a targeted approach through the constituent parts of the virus. Almost all SARS-CoV-2 vaccine candidates currently under development are targeted at the spike (S) protein or its receptor-binding domain (RBD) of the virus. The S protein binds to ACE2, a receptor located on the surface membrane of host cells to initiate the infection process.[12,13] SARS-CoV-2 and SARS-CoV share the same binding receptor in host cells, but the binding affinity of SARS-CoV-2 S protein to ACE2 is about 10–20 times higher than that of SARS-CoV S protein.[14] This might contribute to the higher transmissibility and contagiousness of SARS-CoV-2 as compared to SARS-CoV. The S protein of SARS-CoV-2 is highly glycosylated, and the surface of the virus is covered with glycans; any antibody targeting the S protein will have to get through the glycans before binding to S protein.[15,16]

In addition, the S1 domain of COVID-19 S protein may potentially interact with the human CD26, a key immunoregulatory factor for virulence. SARS-CoV-2 contains other structural antigens such as E (envelope), M (membrane) and N (nucleocapsid) proteins. Their potential in vaccine design has received only limited attention so far. Using reverse vaccinology and machine learning, several research groups attempted to interrogate the viral genomes and proteomes to identify new B- and T-cell epitopes as vaccine antigens.[17,18]

DESIGNING OF SARS-COV-2 VACCINES!

Several recent structural studies have illustrated the molecular binding mechanisms between anti-S-protein antibodies and epitope regions of the S protein. The cross-reactivity of the RBD-specific antibodies with different coronaviruses appears complicated and at least partially depends on the binding targets. It recently demonstrated that a SARS-CoV-specific monoclonal antibody was able to cross-react with SARS-CoV-2, and the binding sites of the two coronaviruses were very similar and highly conservative.[14,15]

Infection with SARS-CoV-2 causes both pulmonary and systemic inflammation, leading to multi-organ dysfunction in patients.[19] Our current understanding of the host immune response against SARS-CoV-2 remains sparse, and the host immune response appears varied with the stage of infection and the severity of disease. Most of the newly discharged COVID-19 patients developed high immunoglobulin G and immunoglobulin M titers to SARS-CoV-2 antigens (especially S-protein RBD and N protein), neutralizing antibodies and cellular immune responses (interferon [IFN]-γ to N protein, main protease and S-protein RBD).[20] The levels of virus-specific T-cell responses waned substantially 2 weeks postdischarge. Detailed analysis of T-cell responses in COVID-19 patients showed that compared with the healthy controls and mild patients, the severe patients showed a significant reduction in the frequency of multifunctional CD4 + T-cells (defined as positive for any two of the cytokines IFN-γ, tumor necrosis factor-α or interleukin-2) as well as a significant increase in the frequency of exhausted (PD1 + CTLA-4 + TIGIT+) CD8 + T-cells.[16,21] The multifunctional CD4 + T-cells have been implicated in the better control of natural infection with human immunodeficiency virus and as a biomarker for vaccine-induced cell-mediated immunity. The excessive exhaustion of CD8+ T-cells in severe patients with COVID-19 may reduce their cellular immune response to SARS-CoV-2.[21] These results have important implications in designing an effective COVID-19 vaccine. The increasing mutagenicity of the virus is still the most challenging factor at this juncture. Developing a single targeted vaccine is not

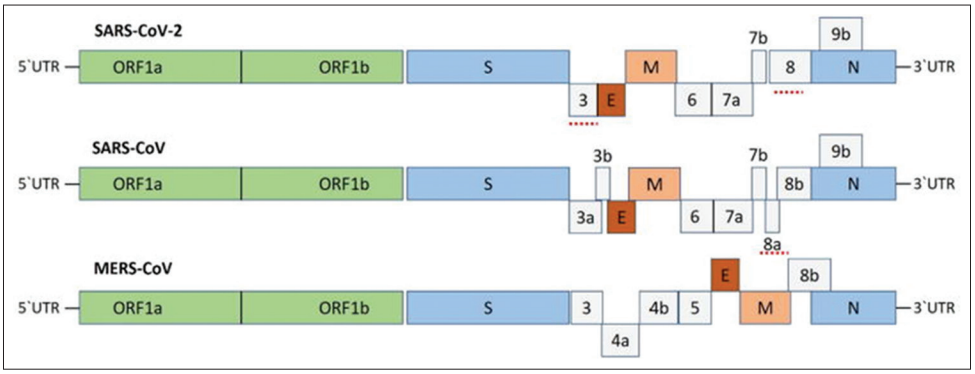

Figure 1: The difference of SARS-CoV-2, SARS-CoV and MERS-CoV vial genome. (Courtesy: Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91-8. Doi: 10.1016/j.jare. 2020.03.005.)

possible owing to the continuous evolving and replication nature of the viral strains and virulence.

THE ULTIMATE RACE OF VACCINES!!

The WHO project under CEPI : Coalition for Epidemic Preparedness Innovations is an innovative partnership between public, private, philanthropic and civil organizations, launched at Davos in 2017, to develop vaccines to stop future epidemics. CEPI has moved with great urgency and in coordination with the WHO in response to the emergence of COVID-19. CEPI has initiated nine partnerships to develop vaccines against the novel coronavirus. The programs are leveraging rapid response platforms already supported by CEPI as well as new partnerships.[22] Currently, more than 150 countries have expressed their interest in developing COVAX (COVID vaccine). The major countries who have launched the research program including the USA, China, Canada, India, Russia, the UK and Western Europe are leading ahead and have already started with clinical trials. Few vaccines have shown exemplified results overlooked globally. The best include Ad5-nCoV (CanSino Biologics), mRNA-1273 (Moderna), AZD1222 (University of Oxford), inactivated vaccine (Wuhan), CoronaVac (Sinovac), BNT162 (Pfizer and BioNTech) and Curevac. This has been summarized in Table 1 (including Indian vaccine trial of COVAX) and is discussed in brief.

CanSino's offering is made from a common cold virus, tweaked to mimic the coronavirus. Sinopharm, a state-owned pharmaceutical company in Beijing, is developing two vaccines made using particles of the coronavirus that have been inactivated. The two vaccines had claimed to produce antibodies in all participants in preliminary Phase I and II trials. Moreover, Beijing-based company Sinovac has announced similarly promising results for its own inactivated-virus vaccine.[23]

Moderna's mRNA-1273, which entered into clinical trials just 66 days after SARS-CoV-2 was first sequenced, showcases the potential for nucleotide-based vaccines. Like traditional live virus vaccines, these vaccines deliver a genetic sequence into a host cell and co-opt host machinery to express antigens of interest. Moderna's vaccine uses a synthetic lipid nanoparticle to carry mRNA templates. Like most other COVID-19 vaccines in development, Moderna's candidate attempts to train the immune system to recognize SARS-CoV-2's spike protein, which the virus uses to bind to and enter host cells.[24]

The University of Oxford and AstraZeneca have embraced a recombinant vaccine called AZD1222 to achieve a similar effect, engineering a chimpanzee adenovirus to carry DNA for the spike antigen. As adenoviruses themselves are immunogenic, such types of approach could generate robust memory B-cell and T-cell responses. In turn it can provide better prophylaxis with fewer doses. It remains to be seen whether mRNA-encoded antigens can confer sufficient protection against pathogens. Earlier attempts with adenovirus vaccines disappointed, at least partly because some recipients had preexisting immunity to the first adenovirus vectors that were trialed. The University of Oxford and AstraZeneca, the first to begin Phase 3 studies, are focusing primarily on healthy adults aged 18–65 years, both who work in frontline health-care settings and the general public. Their 10,000-participant trial is already underway in the UK. The trial is also recruiting a small number of older adults and children to start assessing efficacy in these cohorts.[24] In viral vectors, the genome of one virus is used to deliver the antigen of another virus, thus allowing the development of a platform technology of virus production.[25]

Pfizer and their partner BioNTech forwarded their BNT162b2 mRNA vaccine candidate forward into Phase II/III trial. It comes down to the antigen(s) being coded for. The b1 codes for the coronavirus spike protein's RBD, and this was constructed as a trimmer, three RBDs attached to a "foldon" protein core. Meanwhile, the b2 codes for what they say is an "optimized full-length spike" protein instead, not just the RBD. Pfizer's press release says that both the b1 and b2 candidates induced favorable viral antigen-specific CD4 + and CD8 + T-cell responses, high levels of neutralizing antibody in various animal species and beneficial protective effects in a primate SARS-CoV-2 challenge model. However, they made a choice for the b2 variety partly because it seemed to be better tolerated on injection and also because it led to a wider variety of T-cell responses. These include both CD4 + and CD8 + T-cells, and these were raised not only to recognize the RBD region but also other regions of the spike protein that were not contained at all in the b1 candidate.[26]

The German company, CureVac, is also working on an mRNA vaccine for the new coronavirus. CureVac's experimental rabies vaccine showed a strong immune response with a single microgram of mRNA, which suggested that 1 g could vaccinate 1 million people successfully. However, the factor of effectiveness is still questionable.[27]

Some candidate vaccines are being developed in Russia against COVID19. The Shemyakin and Ovchinnikov

Table 1: Depicts major vaccine trials and their stage of testing

Vaccine	Type	Current phase of testing
Ad5-nCoV (CanSino Biologics)	Adenovirus type 5 vector	Phase 1 and 2 trials
mRNA-1273 (Moderna's)	nucleotide-based vaccines	Phase 2 trials
AZD 1222 (University of Oxford and AstraZeneca)	Adenovirus vaccine	Phase 2b/3 trials
BNT 162 (Pfizer and BioNTech)	mRNA vaccine	Phase 1/2 trials
Unnamed (The Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russia)	Attenuated vaccine	Phase 1/2 trials
COVAXIN (Bharat Biotech; National Institute of Virology, India)	Whole-Virion Inactivated	Phase 1/2 trials

Institute of Bioorganic Chemistry is developing a liposome-encapsulated DNA-protein vaccine based on the COVID-19 spike antigens and its DNA coding sequence and VLP vaccine based on HSB antigen fused with COVID-19 spike antigens. The vaccine candidates against COVID19 based on live attenuated recombinant influenza vector platform are developed by FSBSI "Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of Russian Academy of Sciences" and Smorodintsev Research Institute of Influenza (WHO National Influenza Centre). The FSBSI "Chumakov Federal Scientific Center for Research and Development of Immune-and-Biological Products of Russian Academy of Sciences" is developing two vaccines based on an attenuated and an inactivated strain of the COVID-19 virus isolated in Centre Chumakov (personal communication of Professor Egorov).[25,28]

Bharat Biotech, Serum Institute, Zydus Cadila, Panacea Biotec, Indian Immunologicals, Mynvax and Biological E among domestic pharma firms are working on the vaccines in India. Bharat Biotech has received approval to conduct Phase I and II clinical trial for its vaccine candidate Covaxin that has been developed and manufactured in the company's facility in Hyderabad. It had started human clinical trials. The Phase I and II clinical trials of the vaccine for SARS-CoV-2 by Bharat Biotech have been approved by the Indian drug regulator after preclinical studies demonstrated safety and immune response. The company has developed the vaccine in collaboration with the Indian Council of Medical Research and the National Institute of Virology. Indian Immunologicals, a subsidiary of National Dairy Development Board, has inked an agreement with Australia's Griffith University to develop a vaccine for coronavirus. Others such as Mynvax and Biological E are also working to develop vaccines for COVID-19.[29]

OUR EFFORTS SHOULD BE IMPREGNABLE TO DEVELOP A SAFE VACCINE

A brisk effort of vaccine development against COVID-19 should not be attained by risking lives to further danger. The main reason is that before being put on the market, the vaccine should be safe, both in the short-term and in the long-term effectiveness. In the history of vaccine production, there have been situations of contamination with other viruses, fortunately without major consequences.[30] For example, one-third of the polio vaccines administered in the US between 1955 and 1963 also contained simian virus 40 (SV40), and more recently, rotavirus vaccines have been discovered to also have swine circoviruses.[31-33] In order to avoid risky circumstances, purity has to be checked and then sterile production lines are to provide. This takes time. In rare cases, certain antibodies generated by immunization may promote an aggravated form of the disease (a situation called antibody-dependent enhancement [ADE]).[34] When these antibodies re-establish contact with the virus, they will actually help it enter the cells and cause infection. ADE has been described not only in many viral infections (influenza, dengue, Zika, etc.) but also in coronaviruses. The mechanism of ADE has not been confirmed for coronavirus in humans.[9] Several animal studies have shown that some types of anti-SARS and anti-MERS vaccines, although effective in generating antibodies, can lead to more severe forms of disease when the virus is subsequently inoculated.[35]

The second reason to be considered is that the vaccine must be not only safe but also effective. It must be able to determine the synthesis of antibodies of a certain type at a certain concentration (titer) and to provide protection for a reasonable time.[25] Vaccines never generate immunity to all vaccinated people.[36] The causes are complex and vary from genetic and immunological factors, to the quality of the vaccines themselves and how they are administered. For instance, age is an important aspect, and some influenza studies have shown that aging of the immune system dramatically decreases the effectiveness of vaccination.[37]

In future, any anti-SARS-COV-2 vaccine, should evaluate all these aspects, and the primary immunization failures must be minimized by adjusting the doses or number of administrations. Assuming that the vaccine will generate an effective immune response to a sufficient number of individuals among those vaccinated, the time frame of vaccine protection is questionable.[38] For example, after measles vaccination, a small percentage of those

who initially respond well lose their protective antibody status within a few years, a phenomenon called secondary immunization failure.[39]

CONCLUSION

Developing a vaccine against COVID-19 is of utmost necessity and need of the hour, but comprising the safety of the vaccine can cause more deleterious effects by itself and efficacy for the vaccine is left for time testing. Moreover, the scientific community across the globe agrees on to the short life span of antibodies induced by the COVID-19 infection itself, the immune response induced by the vaccine will be still debatable

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