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COMMENTARY

Promise and challenges in the development of COVID-19 vaccines

Wangxue Chen [a,b]

[a]Human Health Therapeutics Research Center (HHT), National Research Council Canada, Ottawa, Ontario, Canada; [b]Department of Biology, Brock University, St. Catharines, Ontario, Canada

ABSTRACT

The pandemic outbreak of COVID-19, caused by coronavirus SARS-CoV-2, created an unprecedented challenge to global public health system and biomedical community. Vaccination is an effective way to prevent viral infection, stop its transmission, and develop herd immunity. Rapid progress and advances have been made to date in the development of COVID-19 vaccines. Currently, more than 115 vaccine candidates have been developed from different technology platforms with several of them in clinical trials. Most of those vaccine candidates are developed based on the experience with other coronaviruses with an aim to induce neutralizing antibodies against the viral spike protein or its different receptor binding domains. Here, we discuss the promise, potential scientific challenges, and future directions for the development of a safe and effective COVID-19 vaccine. We also emphasize the importance of a better understanding of the infection pathogenesis and host defense mechanisms against SARS-CoV-2 infection.

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Introduction

The outbreak of COVID-19 created an unprecedented challenge to global public health system and biomedical community. The pandemic has now spread to essentially every country, infected millions, and killed hundreds of thousands of people.[1] In response to this extraordinary and urgent health challenge, varying medical interventions, from repurposed antivirals, off label drug prescription, convalescent patient serum, or plasma transfer to mesenchymal stem cell therapies, have been mobilized. Currently, there are no vaccines or specific therapeutics available against SARS-CoV-2, the causative agent of COVID-19.

Vaccination is one of the most effective medical measures for prevention and control of infectious diseases and is viewed by the World Health Organization (WHO) as a key step in the global transition from the current pandemic to business as usual.[2] Indeed, the global COVID-19 vaccine R&D pipeline now includes >115 leading vaccine candidates with eight candidates in Phase 1 or 2 clinical trials and more in the next 3 to 6 months.[3] Almost all traditional (such as attenuated and inactivated, subunit recombinant, viral vectors, and virus-like particles, VLP) and innovative (such as DNA and mRNA) vaccine technology platforms have been deployed.[3,4] In this regard, several recent reviews have elegantly and comprehensively summarized the advantages and disadvantages, the potential production and regulatory challenges, and the anticipated timeline of those platforms.[4–8]

The availability of a safe and effective vaccine will make a remarkable contribution to stop COVID-19 pandemic by preventing the susceptible population from infection and disease, stopping viral transmission, and improving herd immunity. Vaccines are highly cost-effective and are likely to induce both specific antibody and T cell responses. However, the development of new vaccines has historically taken several years (5 y for the Ebola vaccine, and still no vaccines for 2003 SARS or 2012 MERS). With the strong political willingness, substantial financial support, active industrial participation, and the expertise and capacities accumulated from past efforts on developing vaccines against other coronavirus, it is anticipated that a COVID-19 vaccine might be available in ~18 months, as estimated by WHO and other vaccine experts. If achieved, this would be a remarkably shorter time frame relative to any other vaccine that has been developed.

This commentary discusses the potential scientific challenges and future directions for developing a safe and effective COVID-19 vaccine, based on our current knowledge on the pathogenesis of and host defense against SARS-CoV-2 infection.

Vaccine antigen selection and design

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 angiotensin-converting enzyme 2 (ACE2), a receptor located on the surface membrane of host cells to initiate the infection process.[9,10] 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.[11] This might contribute to the higher transmissibility and contagiousness of SARS-CoV-2 as compared to SARS-CoV.

The S protein is a major virulence factor of coronaviruses to enter the host cell. It is highly immunogenic and induces neutralizing antibodies and T-cell responses. To facilitate the

CONTACT Wangxue Chen Wangxue.Chen@nrc-cnrc.gc.ca Human Health Therapeutics Research Center (HHT), National Research Council Canada, Ottawa, Ontario K1A 0R6, Canada

design of SARS-CoV-2 vaccines and therapeutics, several recent structural studies have illustrated the molecular binding mechanisms between anti-S-protein antibodies and epitope regions of the S protein.[11–15] The cross-reactivity of the RBD-specific antibodies with different coronaviruses appears complicated[11,15] and at least partially depends on the binding targets. It was 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. This brings the possibility that antibodies induced by vaccines might be effective in neutralizing multiple current and future pandemic coronaviruses.[15]

Several recent studies on SARS-CoV-2 favor the chance to develop an effective vaccine for this virus. Preliminary analysis of the SARS-CoV-2 genome in Italy identified only five novel variants in local samples, suggesting that the SARS-CoV-2 genome is relatively stable (https://www.biotechniques.com/coronavirus-news/insight-into-sars-cov-2-genome-spells-good-news-for-vaccine-development/), and the virus is inefficient in mutating to evade immune pressure. In addition, as discussed above, neutralizing antibodies induced by vaccines against certain conserved or cryptic epitopes might be effective in neutralizing multiple current and future pandemic coronaviruses.[15] Moreover, vaccines against SARS and MERS are shown to be protective in animal models.[4] On the other hand, the S protein of SARS-CoV-2 is highly glycosylated.[11,14,16] As such, the surface of the virus is covered with glycans and any antibody targeting the S protein will have to get through the glycans before binding to S protein. In addition, the S1 domain of COVID-19 S protein may potentially interact with the human CD26, a key immunoregulatory factor for virulence.[16] Those structural information is very valuable for the design of future COVID-19 vaccines.

In addition to S protein, 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. By 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] In one study, two non-structural adhesins (nsp3 and nsp8) were predicted to have high protective antigenicity. In particular, nsp3 is highly conserved among SARS-CoV-2, SARS-CoV, and MERS-CoV and has not been studied previously. It was proposed that a vaccine containing a cocktail of structural protein-(s) and a non-structural protein(s) would stimulate effective and complementary immune responses.[18] However, the promise of this approach remains to be tested in animal models.

Immune responses to SARS-CoV-2 infection

Infection with SARS-CoV-2 causes both pulmonary and systemic inflammation, leading to multi-organ dysfunction in patients at high risk.[19] Our current understanding of the host immune response against SARS-CoV-2 remains sparse and was largely derived from limited cases of terminal illness or extrapolated from other coronavirus infections. As anticipated, 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 IgG and IgM 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] However, the levels of virus-specific T cell responses waned substantially 2 weeks post-discharge.[20] Detailed analysis of T cell responses in 16 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 (TNF)-α, or interleukin (IL)-2) as well as a significant increase in the frequency of exhausted ($PD\text{-}1^+CTLA\text{-}4^+TIGIT^+$) $CD8^+$ T cells.[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] Those results have important implications in designing an effective COVID-19 vaccine.

Several studies have implicated cytokine storm in the immunopathogenesis of SARS-CoV-2 infection and associated mortality.[21–23] In one study of 12 patients, it was found that 38 out of 48 measured cytokines in the plasma of infected patients were significantly elevated compared to healthy individuals. Seventeen cytokines were linked to the blood viral burdens and 15 cytokines were strongly associated with lung injury and disease severity.[22] On the other hand, SARS-CoV-2 may escape the host immune recognition and attacks by damping the host antiviral cytokine (such as the Type I and Type III IFNs) and chemokine responses.[24]

Protective immunity against SARS-CoV-2 infection

An ideal vaccine should induce the appropriate type of long-lasting, host protective immunity without causing overt adverse reactions. Previous studies with other coronavirus, particularly SARS-CoV and MERS-CoV, showed that neutralizing antibodies to S protein played an important role in the antiviral immunity and have also been presumed as the immune correlates of protection against SARS-CoV-2 infection. However, it is recognized that a mixed, balanced neutralizing antibody and antigen-specific T cell responses are preferred and important for the vaccine to block the viral invasion to host cells and to clear the infected cells.[4]

The recent encouraging results in the use of plasma and sera from convalescent patients for treatment of COVID-19 patients[25,26] supported a potential role of humoral immunity in the protection against SARS-CoV-2 infection. However, the contribution of other components in the transfused plasma and sera cannot be ruled out. It was reported that the reduction in the viral burden and clinical improvement in COVID-19 patients were not always correlated with the serum antibody titers or kinetics.[27] Thus, further information on the correlation between therapeutic efficacies and antibody titers in the transfused plasma and sera will be important. To this end, it is encouraging to see that a multicenter, randomized clinical trial involving 1000 patients has been planned in Canada.

Stimulation and activation of host innate immune responses including innate memory responses may play an important role in SARS-CoV-2 immunity. Previous studies have shown that the innate immune memory induced by mycobacterial pathogens or vaccines provided nonspecific protections against subsequent viral infection.[28] It was proposed that Bacillus Calmette–Guérin (BCG) immunization policies might be associated with the resistance to COVID-19.[29–31] To test this hypothesis, a clinical trial in those with a higher risk of infection (frontline medical staff) and severe diseases (elderly) will start soon in Australia, Netherlands, German, and the United Kingdom.

Development of a safe and effective COVID-19 vaccine is likely to encounter a number of specific challenges. Among them, antibody-dependent enhancement (ADE) of diseases is perhaps one of the leading concerns to vaccine developers and regulatory agencies. ADE has been identified in the development of other vaccines (dengue, respiratory syncytial virus (RSV), Zika, and SARS). It was found that anti-S neutralizing antibody titers in deceased SARS patients were not only significantly higher than in recovered patients but also reached its peak much earlier (Day 14.7 vs Day 20).[32] Subsequent studies in rhesus macaques showed that anti-S-IgG failed to inhibit SARS-CoV infection, and instead exacerbated macrophage-mediated lung damage.[32,33] However, an increased anti-N antibody titer appears to help patients better.[32] Since SARS-CoV-2 and SARS-CoV belong to the same family virus, the potential of ADE is a special concern in COVID-19 vaccine development.

Preclinical evaluation of vaccine efficacies and safety

Several animal models of SARS-CoV-2 infection have been developed and utilized for studying the biology of SARS-CoV-2 and evaluating the immunogenicity, safety, and efficacies of COVID-19 vaccines and therapeutics. Based on the experience with other coronaviruses and the limited knowledge of SARS-CoV-2, animal models using hACE2 transgenic mice, ferrets, non-human primates, and more recently hamsters have been developed. Except the ferret model,[34] no detailed characterization of the animal models has been published. The rapid progress of vaccine candidates from the preclinical studies into clinical trials indicate that those animals are at least susceptible to the infection with clinical strains of SARS-CoV-2. A better characterization and refinement of those models will be needed. It is also crucial that the prevalent viral strains will be used in the challenge and efficacy studies.

The cost, supplies, and potential preexisting antibodies to SARS-CoV-2, as in the case of influenza, render the ferret a less attractive model for initial vaccine candidate screening. Hamsters, which share high ACE2 protein sequence similarity to humans, may be an alternative model.[35] When infected with SARS-CoV-2, all infected animals became sick and developed mean serum neutralizing antibody titer ≥1:427 at 14 d post-infection.[35] The potential of cotton rats as an animal model is warranted for investigation since cotton rats are an excellent model for several respiratory viral infections, notably RSV infection and vaccine-induced ADE.

Despite the rapid progress of several vaccine candidates into Phase I/II clinical trials, very little published preclinical immunogenicity and efficacy data are available for critical analysis. As such, it is not clear to what extent those animal models predict the immunogenicity, efficacy, and safety of the vaccine candidate in humans. In this regard, it remains to be known if a SARS-COV-2 vaccine can be developed successfully until clear clinical proof of principle is obtained, and ideally such proof will come from a placebo-controlled efficacy trial.

In addition to the common hurdles in vaccine development, the successful and rapid development of COVID-19 vaccines might encounter some specific challenges. As discussed above, one of the major challenges is likely to be the potential vaccine-induced ADE. The duration of the vaccine-induced protective immunity is another concern. Limited human clinical data suggest that the antibody responses were sustained for at least 2 weeks after patient discharge but the T cell responses waned rapidly.[20] Several episodes of infection were noted previously in some patients recovered from other coronavirus infections, suggesting the possibility of a short-lived immunity.

The duration and magnitude of vaccine-induced immunity can be improved by the use of adjuvants and additional booster(s). Adjuvants are needed for inactivated or subunit vaccine candidates. For rapid response vaccines, the use of licensed adjuvants will be the preferred choice. However, the pool of such adjuvants is very limited and most of them induce primarily humoral immune responses in humans. Several experimental adjuvants of late stage of preclinical development are available, but the inclusion of those is likely to prolong the time for regulatory approval. Similarly, selection of the booster can generate potential issues for live-attenuated vaccines and viral vector vaccines. The anti-vector immunity induced by the primary immunization may render the booster less effective, unless a heterologous prime-boosting strategy is applied.

Detailed discussion on clinical trial logistics and bottlenecks are out of the scope of this commentary. To expedite the development of COVID-19 vaccines, innovative approaches for clinical trial design and accelerated flexible regulatory approval pathway have been proposed and developed. As such, several vaccine candidates have already entered clinical trials without the full preclinical efficacy data available. Others might seek emergency use of the vaccine for certain populations, such as health-care professionals, before the full completion of clinical trials.

Controlled human challenge trials of SARS-CoV-2 vaccine candidates have been proposed to replace the conventional Phase 3 clinical trial to accelerate the testing and potential rollout of efficacious vaccines. Such an approach might save several months from the licensure process.[36] But others disputed this approach or any regulatory shortcut or speedy up.[37] It is cautioned that the potential safety risks will not only bring unwarranted setbacks for COVID-19 vaccines but also repercussion in the overall vaccine intake by the general public.[37]

Summary and prospective

Built on the prior experience with other coronaviruses and different mature or innovative vaccine platforms, remarkable

progress have been made in the development of COVID-19 vaccines since the submission of the first SARS-CoV-2 genomic sequence data on January 10, 2020. Almost all vaccines under current development target at various forms of S protein or the RBD region. S protein is a key virulence factor of SARS-CoV-2, and the neutralizing antibodies against the prefusion protein are considered the immune correlate of protection. Thus, future studies to identify additional, critical viral-neutralizing epitopes, other viral structure antigens, and T cell epitopes are needed. In addition, continuing search and identification of conserved or cryptic antigen epitopes are warranted for developing pan-coronavirus vaccines against the potential mutation of SARS-CoV-2 and the emergence of new coronavirus strains.

Although several vaccine candidates from different technology platforms have entered into clinical trials, the detailed immunogenicity and protective immunity data are not available. Most strategies and approaches used were extrapolated from other coronavirus studies or the development of other vaccines. Therefore, further understanding the viral pathogenesis and the mechanisms and correlates of immune protection is critical for the development of improved COVID-19 vaccines. Additional efforts are also needed in the development of innovative animal models suitable for screening the efficacy and safety (particularly the ADE) of vaccine candidates to provide a better bridging to human clinical trials. Respiratory tract and airborne infection are the major routes of SARS-CoV-2 infection in humans. Therefore, the potential of mucosal, particularly intranasal or aerosol, immunization needs to be explored for the induction of strong mucosal IgA immune responses. This route of immunization may also reduce the impact of preexisting anti-vector immunity for certain viral vector-based vaccines.

Different vaccine platforms have their own advantages and challenges. The production and regulatory pathway of inactivated or attenuated vaccines are well established but their safety can be a potential concern. Recombinant protein/peptide vaccines and VLP vaccines have excellent safety profiles, but the development of production process and needs for adjuvants may slowdown their clinical trials. The potential of preexisting anti-vector immunity and the induction of new anti-vector immunity for future vaccines are potential challenges of viral vector vaccines. DNA and mRNA platforms have the advantages for rapid development and production of vaccines for pandemic, but currently, there are no approved human vaccines. Therefore, it is unclear which candidate vaccines will prove to be safe and efficacious and when the first COVID-19 vaccine will be licensed and made available for global use. Nevertheless, the readiness of rapid vaccine development and production platforms are critical for future pandemic and epidemic responses.

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Disclosure of potential conflicts of interest

The author declares that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

ORCID

Wangxue Chen http://orcid.org/0000-0003-0958-7728

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