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Perspective

Approaches and Challenges in SARS-CoV-2 Vaccine Development

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SUMMARY

The explosive spread of SARS-CoV-2 suggests that a vaccine will be required to end this global pandemic. Progress in SARS-CoV-2 vaccine development to date has been faster than for any other pathogen in history. Multiple SARS-CoV-2 vaccine candidates have been evaluated in preclinical models and are currently in clinical trials. In this Perspective, we discuss three topics that are critical for SARS-CoV-2 vaccine development: antigen selection and engineering, preclinical challenge studies in non-human primate models, and immune correlates of protection.

INTRODUCTION

SARS-CoV-2 was initially identified as the etiologic agent responsible for a cluster of severe pneumonia cases in Wuhan, China in December 2019 (Chan et al., 2020; Huang et al., 2020; Li et al., 2020; Wu et al., 2020; Zhu et al., 2020c). On March 11, 2020, the World Health Organization (WHO) declared SARS-CoV-2 a global pandemic, and the disease was named COVID-19. In response to this pandemic, industry, government, philanthropy, non-governmental organizations, and academia are collaborating to develop therapeutic and prophylactic countermeasures, including vaccines.

SARS-CoV-2 is a member of the *Coronaviridae* family, joining severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) as coronaviruses causing severe disease in humans. These pathogens are single-stranded, positive-sense RNA viruses and encode four main structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as multiple non-structural proteins (Srinivasan et al., 2020). Similar to SARS-CoV, the SARS-CoV-2 S protein binds angiotensin-converting enzyme 2 (ACE2) as its primary host receptor to mediate viral entry (Hoffmann et al., 2020), and S is the main target for neutralizing antibodies.

SARS-CoV-2 has proven to be highly transmissible, including from asymptomatic and presymptomatic individuals (Arons et al., 2020; McMichael et al., 2020). Currently, at least six vaccine candidates have been tested in non-human primates (NHPs) and have reported either partial or complete protection (Corbett et al., 2020; Gao et al., 2020; Mercado et al., 2020; van Doremalen et al., 2020; Wang et al., 2020; Yu et al., 2020). Moreover, multiple promising vaccine candidates have entered clinical trials, and early phase clinical trial data have also been reported (Folegatti et al., 2020; Jackson et al., 2020; Mulligan et al., 2020; Zhu et al., 2020a). In this Perspective, we focus on three core issues related to SARS-CoV-2 vaccine development: antigen selection and engineering, preclinical challenge studies, and immune correlates of protection. A discussion of clinical development and deployment strategies for SARS-CoV-2 vaccines, while also important, is beyond the scope of this manuscript.

ANTIGEN SELECTION AND ENGINEERING

Coronaviruses Encode Multiple Structural and Non-structural Proteins that Could Potentially Serve as Immunogens for a SARS-CoV-2 Vaccine

The best characterized proteins are S, N, M, and E. S has most commonly been utilized in coronavirus vaccine studies, due to its pivotal role in mediating viral entry into cells (Song et al., 2019). Mature S is a trimeric class I fusion protein located on the surface of the virion. Many coronaviruses proteolytically process S into the S1 and S2 domains. The S1 fragment contains the receptor binding domain (RBD) and the S2 fragment contains the fusion peptide, which are responsible for receptor binding and cell fusion, respectively. For SARS-CoV, S has been demonstrated to be the primary target of neutralizing antibodies. In mouse models of SARS-CoV, passive transfer and vaccine studies have shown that S-specific antibodies confer protective immunity (Enjuanes et al., 2008; Yang et al., 2004). For SARS-CoV-2, studies with monoclonal antibodies have shown that SARS-CoV-2-infected humans develop robust neutralizing antibody responses against S and in particular the RBD (Baum et al., 2020; Hansen et al., 2020; Ju et al., 2020; Rogers et al., 2020; Shi et al., 2020; Zost et al., 2020).

In addition to S, early studies with SARS-CoV suggested that most infected individuals developed an antibody response to N (Pei et al., 2005). N-protein-immunized BALB/c mice also

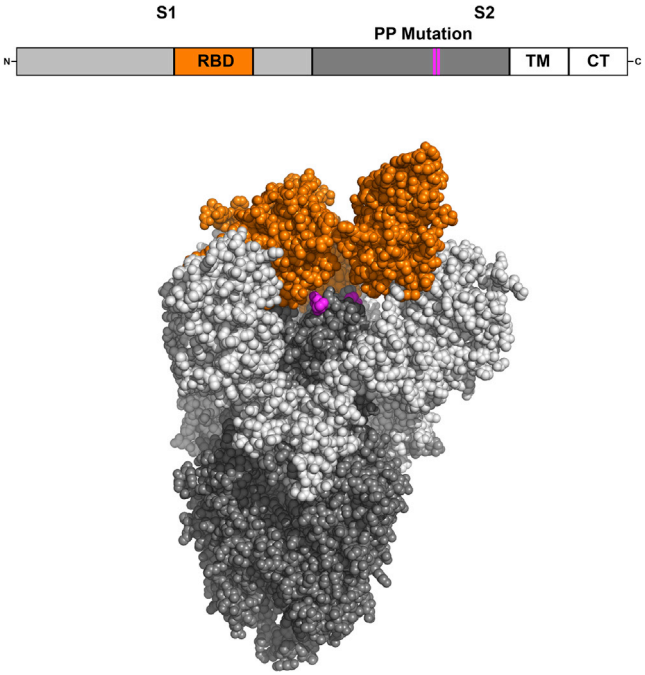

Figure 1. SARS-CoV-2 Spike
Graphical representation of the SARS-CoV-2 S protein sequence and crystal structure of SARS-CoV-2 S protein ectodomain (PDB: 6VSB) (Wrapp et al., 2020) created by using PyMol software. The transmembrane domain and cytoplasmic tail were not crystallized. TM, transmembrane domain; CT, cytoplasmic tail.

induced $CD4^+$ and $CD8^+$ T cells (Liu et al., 2006). However, vaccination with vaccines expressing N resulted in no protection against SARS-CoV challenge as well as enhanced infection, which was characterized by increased pulmonary eosinophil infiltration (Deming et al., 2006). Passive transfer of anti-N antibodies did not generate an enhanced response, leading the authors to believe that the increased severity was linked to a T cell response (Deming et al., 2006). This was shown upon vaccination with VV expressing S, M, N, and E, as well as VV expressing N, causing the authors to trace back the response to nucleocapsid as an immunogen. Similarly, BALB/c mice vaccinated with a vaccinia virus (VV) expressing N showed enhanced viral infection upon SARS-CoV challenge, which was associated with a T_h2 response with pulmonary infiltration of neutrophils, eosinophils, and lymphocytes (Yasui et al., 2008).

The M and E proteins have garnered less interest as vaccine targets due to lower immunogenicity (Du et al., 2008a), although SARS-CoV patient sera has been shown to be reactive to M peptides (Wang et al., 2003). Of the less-studied proteins, Orf3a has been shown to be capable of raising a neutralizing polyclonal antibody response in rabbits (Akerström et al., 2006).

Currently, Most Vaccines for SARS-CoV-2 Are Focused on S

To target the SARS-CoV-2 S protein in its native prefusion form, antigen stabilization strategies have been used (Figure 1). For MERS-CoV and SARS-CoV, introduction of two prolines in the S2 subunit effectively stabilized the S in its prefusion conformation (Pallesen et al., 2017). The prefusion-stabilized MERS-CoV S generated higher neutralizing antibody titers when compared to native S trimer (Pallesen et al., 2017). This mutation prevented conformational changes of S in the presence of its receptor, *ACE2*, or trypsin (Kirchdoerfer et al., 2018). This stabilization method has also been demonstrated to stabilize the SARS-CoV-2 S (Wrapp et al., 2020) and has been applied to multiple SARS-CoV-2 vaccine candidates (Corbett et al., 2020; Jackson et al., 2020; Mercado et al., 2020). Unlike SARS-CoV, but similar to MERS-CoV, SARS-CoV-2 includes a furin cleavage site between the S1 and S2 domains. For MERS-CoV, researchers mutated the furin cleavage site to enhance homogeneity and stability (Walls et al., 2019). Some investigators have also added a foldon trimerization tag to the C terminus (Walls et al., 2020), and deletion of the cytoplasmic tail of the SARS-CoV S has been shown to increase neutralizing antibody titers (Yang et al., 2004). Current vaccine candidates in clinical trials are also exploring the inclusion of a tissue plasminogen activator leader sequence (tPA) with S (Folegatti et al., 2020; Mercado et al., 2020; Zhu et al., 2020a; Zhu et al., 2020). The tPA leader can increase immunogen secretion and elicit increased humoral immune responses in influenza (Luo et al., 2008) and HIV vaccines (Wallace et al., 2013), although cellular immunogenicity was only increased in the influenza vaccine.

The RBD alone has also been explored as an immunogen. In preclinical studies in mice, rabbits, and monkeys, vaccination with modified vaccinia Ankara (MVA) expressing the full-length SARS-CoV S induced neutralizing antibodies that targeted RBD (Chen et al., 2005). Moreover, depletion of RBD-specific antibodies significantly reduced convalescent plasma neutralizing capabilities (He et al., 2005), consistent with the concept that RBD is the primary target of S-specific neutralizing antibodies. When rabbits were immunized with a variety of SARS-CoV-2 S immunogens, including RBD, S1, S2, and modified variants, RBD was found to elicit five-fold higher affinity antibodies than the other immunogens (Ravichandran et al., 2020). Sprague-Dawley rats immunized with SARS-CoV-2 RBD also elicited a strong neutralizing antibody response (Quinlan et al., 2020). RBD immunogens have been combined with a foldon trimerization tag in the BNT162b1 COVID-19 RNA vaccine candidate (Mulligan et al., 2020).

We recently compared a series of SARS-CoV-2 S immunogens in the context of both DNA vaccines and Ad26 vectors (Mercado et al., 2020; Yu et al., 2020). DNA vaccines encoding the full-length S elicited higher neutralizing antibody titers than did DNA vaccines encoding several S deletion mutants and also afforded improved protection against SARS-CoV-2 challenge in rhesus macaques (Yu et al., 2020). Ad26 vectors were also generated encoding a series of S variants, and the full-length S with the PP-stabilizing mutations proved the most immunogenic and afforded the best protection against SARS-CoV-2 challenge in rhesus macaques (Mercado et al., 2020).

PRECLINICAL CHALLENGE STUDIES IN NHPs

An optimal model for SARS-CoV-2 infection studies would involve an animal species permissive to viral replication and that develops pathologic and clinical features consistent with the human disease. Clinical manifestations of COVID-19 in

Table 1. NHP Challenge Studies of SARS-CoV-2 Vaccine Candidates

Vaccine Name	Vaccine Type	Vaccine Immunogen	Vaccine Dose	Number of Injections	Challenge Route	Reference
PiCoVacc	inactivated	whole virus	3 or 6 μg	3	intratracheal	Gao et al., 2020
BBIBP-CorV	inactivated	whole virus	2 or 8 μg	2	intratracheal	Wang et al., 2020
DNA-S	DNA	engineered S	5 mg	2	intranasal and intratracheal	Yu et al., 2020
mRNA-1273	RNA	engineered S	10 or 100 μg	2	intranasal and intratracheal	Corbett et al., 2020
ChAdOx1 nCoV-19	adenoviral vector	tPA-S	$2.5x10^{10}$ VP	1 or 2	intranasal, intratracheal, ocular, and oral	van Doremalen et al., 2020
Ad26.COV2.S (Ad26-S.PP)	adenoviral vector	engineered S	$1x10^{11}$ VP	1	intranasal and intratracheal	Mercado et al., 2020

humans are usually mild but can include cough, fever, pneumonia, and occasionally respiratory failure and death (Yang et al., 2020). NHPs have significant genetic homology to humans and are often useful models for infectious diseases, although cost and availability can be limiting. In both rhesus and cynomolgus macaques, virus shedding could be detected in nasal, throat, and rectal swabs and in bronchoalveolar lavage for approximately 2 weeks after infection with SARS-CoV-2 using either intratracheal and intranasal infection or intratracheal, intranasal, ocular, and oral infection (Chandrashekar et al., 2020; Munster et al., 2020; Rockx et al., 2020). Early data suggest the utility of both macaque species as animal models for SARS-CoV-2 infection, although respiratory disease has been reported to be mild. The potential utility of African green monkeys as a model is also being explored. We recently demonstrated that SARS-CoV-2 infected macaques were also robustly protected against re-challenge, demonstrating natural protective immunity (Chandrashekar et al., 2020).

At least six SARS-CoV-2 vaccine challenge studies in macaques have been published at the time of this writing (Corbett et al., 2020; Gao et al., 2020; Mercado et al., 2020; van Doremalen et al., 2020; Wang et al., 2020; Yu et al., 2020) (Table 1). These vaccine studies in NHPs have included inactivated vaccines (PiCoVacc [Gao et al., 2020], BBIBP-CorV [Wang et al., 2020]), DNA vaccines (Yu et al., 2020), RNA vaccines (mRNA-1273 [Corbett et al., 2020]), and adenovirus-based vaccines (ChAdOx1 [van Doremalen et al., 2020], Ad26 [Mercado et al., 2020]). PiCoVacc and BBIBP-CorV are based on SARS-CoV-2 CN2 and SARS-CoV-2 HB02 strains, respectively. The viruses were grown in Vero cells and inactivated by using β-propiolactone and were evaluated as two- or three-shot immunization regimens (Gao et al., 2020; Wang et al., 2020). The DNA and mRNA-1273 vaccines encoded stabilized S immunogens and were tested as two-shot immunization regimens (Yu et al., 2020; Corbett et al., 2020). The ChAdOx1 vaccine expressed a codon-optimized full-length S with a human tPA leader sequence and was tested as a single-shot and a two-shot vaccine regimen (van Doremalen et al., 2020). The optimal Ad26 vaccine expressed a prefusion-stabilized S immunogen and was tested as a single-shot vaccine (Mercado et al., 2020).

After vaccination, macaques were challenged by SARS-CoV-2 by the intratracheal, intranasal, oral, and/or ocular routes. Efficacy was determined in these studies by assessment of viral loads in the upper and lower respiratory tracts. Most studies are now focusing on analysis of subgenomic RNA rather than genomic RNA (Wölfel et al., 2020), because subgenomic RNA is believed to be more reflective of replicating virus, rather than input challenge virus. The inactivated vaccine PiCoVacc resulted in reduced viral loads in throat swabs (Gao et al., 2020). The inactivated vaccine BBIBP-CorV also decreased viral loads in throat swabs (Wang et al., 2020). The DNA vaccine encoding the full-length S resulted in >3.1 and >3.7 $\log_{10}$ reductions in median subgenomic RNA levels in BAL and nasal swabs, respectively (Yu et al., 2020). The mRNA-1273 vaccine resulted in undetectable subgenomic RNA in lungs in all but one macaque, and more rapid clearance of virus from nasal swabs (Corbett et al., 2020). The optimal Ad26-S.PP vaccine resulted in undetectable subgenomic RNA in lungs and only one breakthrough in nasal swabs (Mercado et al., 2020). The ChAdOx1 vaccine resulted in reduced subgenomic RNA in BAL but no decrease in nasal swabs (van Doremalen et al., 2020).

The different challenge doses, strains, routes, and assays that were utilized make direct comparisons among these studies difficult. Nevertheless, these studies provide a substantial amount of preclinical data demonstrating protective efficacy of multiple vaccine candidates in NHPs. These data help inform the ongoing clinical development programs for these vaccines. A limitation of all these studies is that macaques do not develop severe disease, respiratory failure, or death. Small animal models are currently being developed that could model severe disease, including hamsters and transgenic mice.

IMMUNE CORRELATES OF PROTECTION

Determining immune correlates of protection (CoP) for SARS-CoV-2 will be critical for guiding vaccine development. Currently, mechanistic CoP for SARS-CoV-2 have not yet been fully determined, although several studies point to the importance of both humoral and cellular immunity.

Humoral Immunity

Neutralizing antibodies (nAbs) represent a commonly studied immune correlate of protection. Early human challenge studies reported that volunteers with higher pre-existing anti-CoV 229E nAb titers (> 5) demonstrated lower proportions of virus isolation and upper respiratory infection than those with low neutralizing titers (≤5) (Bradburne et al., 1967). Pre-challenge serum antibody titers were also negatively associated with upper respiratory infections, nasal virus shedding, and disease severity (Barrow et al., 1990; Callow, 1985). Passive administration of convalescent sera, purified IgG, or monoclonal antibodies have also been shown to suppress SARS-CoV challenge/infection

and associated disease progression in mice, hamsters, ferrets, and humans (Cheng et al., 2005; Roberts et al., 2006; Subbarao et al., 2004; Sui et al., 2005; Yuan et al., 2015).

For SARS-CoV-2, neutralizing monoclonal antibodies isolated from convalescent COVID-19 patients have been shown to inhibit SARS-CoV-2 infection in both prophylactic and therapeutic settings in rhesus macaques and hamsters (Rogers et al., 2020; Shi et al., 2020; Zost et al., 2020). We also reported that DNA vaccines and Ad26-based vaccines induced nAbs that strongly correlated with a reduction of viral loads in rhesus macaques (Mercado et al., 2020; Yu et al., 2020). SARS-CoV-2 inactivated virus vaccines and mRNA vaccines also induced nAbs and conferred protection in macaques (Corbett et al., 2020; Gao et al., 2020; Wang et al., 2020). Collectively, these studies suggest that nAb titers could serve as a useful biomarker for evaluating SARS-CoV-2 vaccines in both preclinical and clinical studies, although these correlates need to be confirmed in humans.

A question that has been raised is whether sub-neutralizing levels of antibodies could have detrimental effects. A prior study revealed that a vaccinia vector-based vaccine expressing feline coronavirus S induced low titers of neutralizing antibodies, which led to early cat mortality upon challenge (Vennema et al., 1990). Consistent with this observation, several studies observed enhanced respiratory disease (ERD) in response to SARS vaccines when antibodies had suboptimal potency or low binding affinity (Jaume et al., 2011; Wan et al., 2020; Wang et al., 2014). A major effort in the field will therefore be the development of animal models for ERD for SARS-CoV-2.

In addition to neutralization, emerging evidence suggests that certain antibody Fc-mediated functionscould also contribute to protective efficacy (Yu et al., 2020), including antibody-dependent complement deposition (ADCD), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent NK cell activation (ADNKA) (Zohar and Alter, 2020). Mucosal immunity is also likely important for protection, because coronavirus infection occurs in the respiratory tract and potentially in the gastrointestinal tract (Xiao et al., 2020). Pulmonary immunoglobulin (Ig)A was observed to be inversely associated with MERS-CoV infectivity in humans (Muth et al., 2015), and animal studies have highlighted the potential role of mucosal immunity in defending SARS-CoV infection (Du et al., 2008b; Huang et al., 2009). Given that intranasal administration could induce stronger mucosal immunity in the respiratory tract than parenteral routes, it could prove useful to evaluate intranasal routes for vaccines (Roper and Rehm, 2009).

Cellular Immunity

Cellular immunity also appears important in the control of coronavirus infections. Current evidence suggests that not all patients develop protective humoral immune responses, and asymptomatic patients or individuals with mild disease typically develop robust T cell responses (Mathew et al., 2020; Sekine et al., 2020). In a mouse model, SARS-CoV-specific $CD8^+$ T cell numbers correlated with virus clearance and increased survival (Zhao et al., 2010). In addition, memory $CD4^+$ T cells were associated with protective immunity against MERS-CoV (Zhao et al., 2016). Recent studies have reported that neutralizing antibody titers correlated with SARS-CoV-2-specific T cell responses (Ni et al., 2020) and that IgG and IgA antibody titers correlated with S-specific $CD4^+$ T cell responses (Grifoni et al., 2020), suggesting that T cells could indirectly modulate the virus infection by orchestrating antibody production. However, in DNA vaccine studies in mice and NHPs, T cell responses did not correlate with protection (Yang et al., 2004; Yu et al., 2020). Nevertheless, severe patients tend to have a higher frequency of polyfunctional CD4 cells expressing interferon (IFN) γ, interleukin (IL)-2, and tumor necrosis factor alpha (TNF-α) (Sekine et al., 2020; Thieme et al., 2020), although it is possible that these high-frequency T cells could simply represent long-term viral exposure (Altmann and Boyton, 2020).

Innate Immunity

There is limited data on innate immune correlates of protection. Existing pathogenesis studies suggest that the excessive production of proinflammatory cytokines and chemokines (cytokine storm) is associated with poor clinical outcome (Channappanavar and Perlman, 2017). IFN-I and IFN-III have shown to be able to suppress SARS-CoV-2 infection *in vitro* (Sallard et al., 2020; Stanifer et al., 2020) and could represent innate immune responses that assist in controlling SARS-CoV-2 infection. Blocking IFN-I signaling in mice has been shown to increase viral load and mortality for SARS-CoV and MERS-CoV (Channappanavar et al., 2019; Frieman et al., 2010). Retrospective cohort studies have also suggested that induction of IFNs correlated with disease severity and viral load in both SARS and MERS patients (Cameron et al., 2007; Kim et al., 2016). It is possible that early induction promotes viral clearance, whereas delayed IFN responses can cause viral persistence, inflammation, and immunopathology (Park and Iwasaki, 2020).

The potential off-target effects of BCG, historically used as a vaccine for tuberculosis, and other live attenuated organisms are also being explored for SARS-CoV-2 (Curtis et al., 2020). Trained immunity is regarded as immunological memory in the innate immune system and likely mediated by epigenetic modifications (Netea et al., 2016). If non-specific trained innate immunity protects against SARS-CoV-2, this would provide an intriguing alternate to antigen-specific vaccination.

CONCLUSIONS

A vaccine will likely be required to end the global SARS-CoV-2 pandemic (Lurie et al., 2020). A successful vaccine will need to be safe, effective, durable, and deployable to large populations. There are currently at least 40 SARS-CoV-2 vaccine clinical trials ongoing. Most vaccine strategies aim to generate S-specific neutralizing antibodies, and preclinical studies have shown substantial protection against SARS-CoV-2 challenge in NHPs. Over the next several months, additional preclinical efficacy studies as well as studies on enhanced respiratory disease will likely be reported, and multiple large-scale clinical efficacy trials will be conducted.

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DECLARATION OF INTERESTS

Correspondence and requests for materials should be addressed to D.H.B. (dbarouch@bidmc.harvard.edu). D.H.B. is a co-inventor on provisional vaccine patents (62/969,008; 62/994,630) that have been licensed.

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