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Forum

Developing pan-β-coronavirus vaccines against emerging SARS-CoV-2 variants of concern

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The concurrent prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV) raises the concern for the emergence of potential new β-CoV clades via genetic recombination, bearing high SARS-CoV-2-like transmissibility and high MERS-CoV-like mortality rates. Therefore, we argue that there is an urgent need to develop pan-β-CoV vaccines that can target not only current SARS-CoV-2 variants of concern, but also future putative SARS-CoV-3- or MERS-CoV-2-like coronavirus.

The development of effective vaccines was considered by some as potentially bringing a quick end to the economic and social ravages of the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2. However, since the end of 2020, many SARS-CoV-2 variants of concern (VOCs), such as the Beta and Delta variants, have emerged. These VOCs have shown neutralization resistance to post-vaccination sera in humans and animal models and raised concerns over the apparent waning of protective immunity for the first-generation COVID-19 vaccines that were authorized for emergency use. This cast a shadow over previous expectations. A recent study showed that vaccine efficacy against infections of the Delta variant declined from 93% to 53% at only 4 months post-vaccination in humans [1]. Moreover, SARS-CoV-2 is feared to further mutate into escape variants under the selection pressure of antibodies in COVID-19 convalescents and vaccinees, such as the VOC Omicron (B.1.1.529), which harbors 32 mutations in the Spike protein, the latest SARS-CoV-2 VOC that was first reported to the World Health Organization (WHO) from South Africa on 24 November 2021 [2]. Many groups are investigating this rapid mutagenesis phenomenon by analyzing the impact of such mutants on viral entry and replication and neutralization by antibody or vaccine-induced immune responses, as well as cellular and tissue tropism. It is not hard to envision a case where SARS-CoV-2 or MERS-CoV may further evolve into a new clade, SARS-CoV-3 or MERS-CoV-2, respectively, by genetic recombination between SARS-CoV-2 and MERS-CoV. We know that SARS-CoV-2 and MERS-CoV are concurrently prevalent in the Arabian Peninsula and that genetic recombination can occur on the infection and replication of both SARS-CoV-2 and MERS-CoV in the same host, given that both viruses can infect the same cell (type-II alveolar) and they use identical transcription regulatory sequences, conserved sequences upstream of open reading frames that can mediate discontinuous transcription of the viral genome [3,4]. Moreover, the receptor-binding domain (RBD) of SARS-CoV-2 can putatively bind to dipeptidylpeptidase 4 (DPP4), the MERS-CoV receptor, based on bioinformatics analysis combining human–virus protein interaction prediction and protein docking [5]. Several cases of SARS-CoV-2 and MERS-CoV co-infection have been reported in Saudi Arabia [6], with a foreboding possibility of recombination between these two viruses.

Historically, SARS-CoV-2 was thus named based on phylogenetic analysis, which suggests that it forms a sister clade with human SARS-CoV and bat SARS-related coronavirus (SARSr-CoV) prototypes (Figure 1) [7]. Following this logic, a novel SARS-CoV-3 could emerge if SARS-CoV-2 obtains a genomic segment from MERS-CoV. In addition, presumably, SARS-CoV-3 might preserve the high transmissibility potential of SARS-CoV-2 but acquire the high case-fatality rate (CFR) (35%) of MERS-CoV, whereas the global CFR of SARS-CoV-2 is about 2% based on the information reported by the WHO (https://covid19.who.int/). Similarly, a MERS-CoV-2 might preserve the high CFR of MERS-CoV, while potentially gaining the higher transmissibility rate of SARS-CoV-2. Such a hypothesis calls for the urgent development of pan-β-CoV vaccines that could combat any possible development of future SARS-CoV-3 or MERS-CoV-2.

Currently, many research groups are working on the development of CoV vaccines that are cross-reactive to sarbecovirus, lineage B of the Betacoronavirus genus (primary-level breadth), including SARS-CoV, SARS-CoV-2, and SARSr-CoVs. One study, for example, reported that mosaic nanoparticles comprising the RBDs of four to eight distinct zoonotic coronaviruses, including SARS-CoV, SARS-CoV-2, and some SARSr-CoVs from bats, elicited cross-reactive immune responses against these coronaviruses in mice [8]. Although the RBD of coronaviruses mutates frequently, recent work from our laboratory showed that the neutralizing antibodies (NAbs) induced by SARS-CoV-2 RBD linked to a human IgG Fc fragment (RBD-Fc) cross-neutralized infection by sarbecoviruses, including SARS-CoV, SARS-CoV-2, and some SARSr-CoVs from bats, in mice [9]. Moreover, another group demonstrated that the immunization of macaques with SARS-CoV-2 RBD-conjugated nanoparticles elicited cross-NAb responses against bat coronaviruses, SARS-CoV, and SARS-CoV-2 [10]. In addition, another

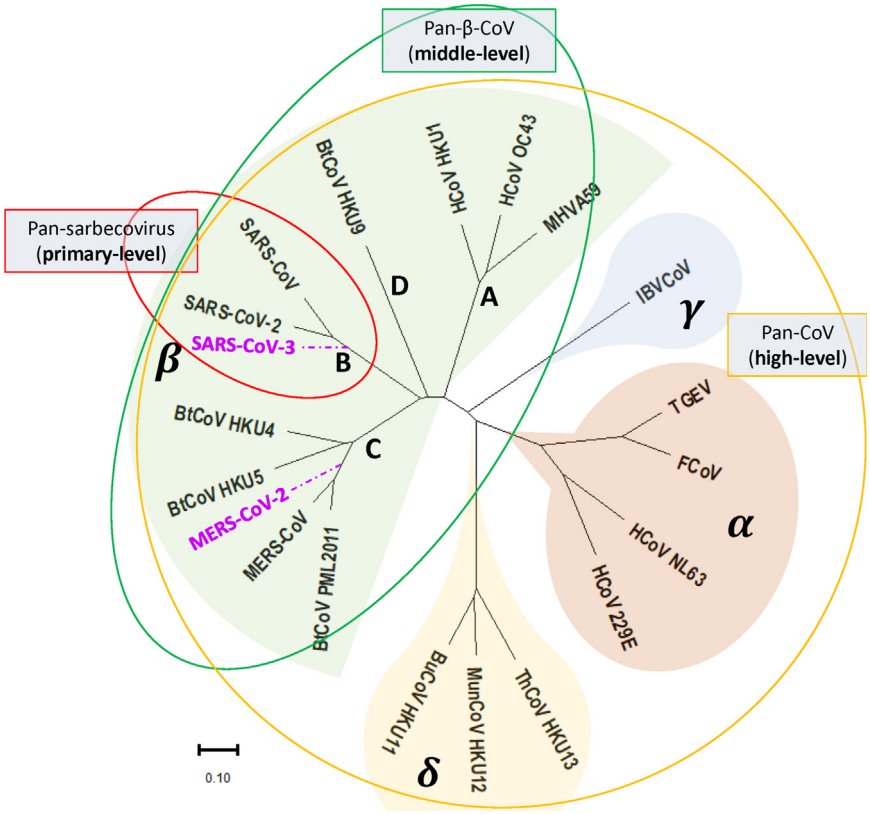

Figure 1. Phylogenetic tree of coronaviruses. Viruses in *Coronaviridae* are divided into four genera: Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV), and Deltacoronavirus (δ-CoV). Sarbecovirus is the B lineage of the β-CoV that might emerge in the near future by genetic recombination and could hypothetically be termed severe acute respiratory syndrome coronavirus 3 (SARS-CoV-3) or Middle East respiratory syndrome coronavirus 2 (MERS-CoV-2).

study reported the development of a SARS-CoV-2 Spike protein ferritin nanoparticle (SpFN) vaccine, formulated with a liposomal adjuvant, that induced highly potent and broad NAb responses against the SARS-CoV-2 variants and SARS-CoV in nonhuman primates [11]. This SpFN vaccine entered a Phase I clinical trial in March 2021 (NCT04784767)[i]. Furthermore, others have documented the presence of potent cross-clade pan-sarbecovirus NAbs in the sera of SARS-CoV survivors immunized with an mRNA (BNT162b2) vaccine [12], indicating that sequential administration of SARS-CoV and SARS-CoV-2 vaccines might be a putative approach to achieving a pan-sarbecovirus vaccine – a possibility that will require robust assessment.

According to the protection range of a certain vaccine, we divided the coronavirus vaccines into three levels (Figure 1). The vaccines that can protect against infection with all sarbecoviruses, all Betacoronaviruses, and all coronaviruses fall into primary-level, middle-level, and high-level breadth, respectively. We argue that these efforts can result in successful pan-sarbecovirus (primary-level breadth) vaccines. However, as hypothesized in the preceding text, a pan-β-CoV vaccine (middle-level breadth) is urgently needed to curtail the potential pandemic tide of a likely SARS-CoV-3 or MERS-CoV-2. Of note, SARS-CoV-2-reactive $CD4^+$ T cells have been detected in the blood of around 35% of unexposed healthy individuals; moreover, *in vitro* analyses have shown that the numbers of activated $CD4^+$ T cells increase after the incubation of isolated SARS-CoV-2-specific $CD4^+$ T cells with peptides derived from the Spike proteins of human endemic coronavirus 229E (belongs to α-CoV; Figure 1) and OC43 (belongs to β-CoV), indicating that SARS-CoV2-specific $CD4^+$ T could also respond to coronaviruses from other genera [13]. This study suggests the presence of cross-reactive $CD4^+$ T cells that might be induced by other coronaviruses in human blood. However, this does not mean that pan-coronavirus vaccine (high-level breadth) could become available based on the induction of cross-reactive $CD4^+$ T cells.

First, rare evidence suggests that T cell responses can correlate with protection; however, many studies have shown that NAb titers induced by vaccines positively correlate with protection against symptomatic and asymptomatic SARS-CoV-2 infection in vaccinated subjects [14]. Second, T cell immune-based pan-CoV vaccines with low neutralization immunogenicity may induce a suboptimal concentration of NAbs that may enhance SARS-CoV-2 infection by antibody-dependent enhancement (ADE) of viral entry [15], despite the fact that researchers have reported findings in which non-NAbs that show ADE *in vitro* can still protect against SARS-CoV-2 replication in monkeys and mice [16]. Therefore, while chasing pan-β-CoV vaccines, taking into account both the titer of NAbs and the T cell responses induced by vaccines will be an important measure for efficacy and safety, moving forward.

We posit that it may be more realistic to develop a middle-level-breadth vaccine (i.e., pan-β-CoV vaccine) than a high-level vaccine (i.e., pan-CoV vaccine against

the currently circulating SARS-CoV-2 and MERS-CoV as well as their variants and possible related new clades; e.g., SARS-CoV-3, MERS-CoV-2) to be able to equip ourselves for the possible emerging SARS-CoV-2 VOCs and SARS-CoV-3 or MERS-CoV-2 outbreaks.

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Declaration of interests

The authors declare no interests.

Resources

[i]https://clinicaltrials.gov/ct2/show/NCT04784767

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