Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Immediate need for next-generation and mutation-proof vaccine to protect against current emerging Omicron sublineages and future SARS-CoV-2 variants: An urgent call for researchers and vaccine companies – Correspondence

Dear Editor

Several variants of SARS-CoV-2 have emerged after its first infection was reported in December 2019. The world has noted significant variants from time to time, such as B.1.351 (Beta; originated from South Africa during May 2020), B.1.1.7 (Alpha; originated from the UK during September 2020), B.1.617.2 (Delta; originated from India during October 2020), P.1 (Gamma; originated from Brazil in November 2020), and B.1.1.529 (Omicron; originated from multiple countries during November 2021). WHO has designated the significant variants concerning the epidemiology blueprint and virulence pattern into two main categories, i.e., VOCs and VOIs. Variants such as Beta, Delta, Alpha, Gamma, and Omicron are now categorized as previously circulating VOCs. Similarly, numerous VOIs also have been reported earlier from time to time, including B.1.525 (Eta), C.37 (Lambda), B.1.526 (Iota), P.2 (Zeta), Mu (B.1.621, B.1.621.1) etc., [1,2].

The world population is experiencing ongoing surges of the recent SARS-CoV-2 variant, Omicron, and its sublineages. WHO was informed about the Omicron variant identification on November 24, 2021, within two days, WHO categorized this new variant as VOC due to its high transmission capacity, immune escape, and vaccine escape. Flemming A. concluded this variant to be a prominent variant for escape events [3]. Different studies have shown that very negligible to untraceable levels of nAbs were found against Omicron. The studies used nAb from fully vaccinated individuals or sera from convalescent plasma from COVID-19 vaccinated individuals. All the studies used different vaccines such as mRNA-1273, BNT162b2, BBIBP-CorV or Sputnik V, ChAdOx1-nCoV19, or Ad26.COV2.5 to illustrate the vaccine escape [3]. Cao et al. found that Omicron can escape the majority of the nAbs of the SARS-CoV-2. They also found the nAb escape mutations of Omicron, and that Q493R, E484A, K417N, and G446S can escape groups A to D nAbs. Similarly, group F nAbs were escaped by S371L, N440K, and G339D [4]. The study by Planas et al. concluded that Omicron could escape a larger amount of vaccine-elicited antibodies and most of the therapeutic monoclonal antibodies. In this study, the researchers collected sera from COVID-19-convalescent patients after 6–12 months of infection with symptoms. The study showed very low, or no neutralizing activity to be observed against the Omicron variant [5]. We also found some RBD mutations; one non-RBD mutation of Omicron can help escape the antibodies. Among them, seven mutations are from RBD and one from outside RBD. The seven RBD mutations are G496S, S477N, K417N, E484A, Q493K, Y505H, and N501Y, and the one outside RBD mutation is D614G [6]. Chen et al. also found mutational escape of the Omicron variant. They have considered 15 RBD mutations of Omicron and found antibody resistance properties of the Omicron using the AI model. Finally, researchers have urged for a mutation-proof SARS-CoV-2 vaccine [7].

If we look at all the significant variants like Alpha to Omicron, escape mutation is a crucial factor for the SARS-CoV-2 variants. Escape mutations are responsible for immune escape and partial or complete vaccine escape in most of the variants, and lead to breakthrough infections owing to complete and/or partial vaccination failure. Therefore, there is an immediate need for designing and developing the next-generation and mutation-proof vaccines to provide effective protection against emerging Omicron sublineages and to tackle the future SARS-CoV-2 variants and lineages. For this purpose, researchers must identify and list all the important vaccine escape mutations or nAb escape mutations. All these mutations must be considered during development of the mutation-proof vaccine construct.

Previously, we have also developed a multi-epitopic, next-generation vaccine construct using the common T-cell and B-cell epitopes, which were collected from four variants: Wuhan variant, B.1.351 (Beta), B.1.1.28 (P2, Zeta), and B.1.1.7 (Alpha). In this vaccine construct, we have considered K417N, T716I, N501Y, S982A, A570D, L18F, P681H, D614G, D1118H, T1027I, P681H, E448K, H655Y mutations. This may be one of the significant mutation-proof, multi-epitopic, next-generation vaccine construct [8]. However, after the Omicron variant's origin and emergence along with its multiple lineages/sub-variants, it is now quite apparent that all the new and the next variants are higher versions of the previous variants in terms of gaining better immune escape properties and transmission characteristics, and acquiring more mutations. That is why, Omicron gained more mutations to become a better and a more efficient version concerning immune escape, nAb escape, and bypass vaccine-induced protective immunity compared to the immediate previous variant (Delta). Several Omicron sublineages have been reported recently, such as BA.1, BA.2, BA.2.75, BA.2.12.1, BA.3, BA.5, and BA.4. Among these, emerging sublineages, BA.2.75, BA.2.12.1, BA.5, and BA.4. are listed by WHO as the "Omicron subvariants under monitoring" [2]. Some researchers have already stated that BA.2 is one of the new dominating sublineages due to its importantly acquired antibody-resistant characteristics and vaccine escape properties. Considering the S-protein mutation, these researchers have calculated the BFE changes induced by mutations and concluded that BA.2 might be the new dominating sublineage [9]. Many researchers evaluate SARS-CoV-2 variants/sublineages on the different properties regarding nAb escape or vaccine escape by considering presence of significant mutations. They must consider all the mutations of previous VOCs, VOIs, and recent sublineages of Omicron. Finally, researchers should list the significant mutations and consider them for effective vaccine development against the emerging SAR-CoV-2 variants. It is a challenging task to list all the emerging mutations. A mutation list of S-protein has been

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prepared in considering RBD mutation, NTD mutations, and non-NTD or non-RBD mutations, and all these mutations have been represented by using a ribbon structure of S-protein (Fig. 1). AI can be a helpful tool for researchers to select significant mutations for progressing towards development of future mutation-proof vaccine construct.

The scientific community is proud of its success stories in developing the COVID-19 vaccine. Previously, no other vaccine has been developed for any infectious disease with such speed. For the first time, the world has seen the COVID-19 vaccine crossed the process of "bench to clinic" within a year [10]. The COVID-19 vaccine developmental efforts have been outstanding with public-private partnerships and they are excellent examples of collaborative effort [11]. The time has now come to make further high efforts to promote needful collaboration among researchers and vaccine companies to develop the most effective vaccines. These efforts hopefully can counteract the ongoing COVID-19 pandemic more effectively. The world is looking for a new or modified, next-generation, and mutation-proof vaccine for pan-SARS-CoV-2 variants coverage to protect against all the VOCs, VOIs, and VUMs. We urge for the earliest development of a priority vaccine to counteract SARS-CoV-2 and its multiple future variants.

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Data statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

List of abbreviations

VOC	Variants of concern
VOI	Variants of interest
nAb	neutralizing antibodies
AI	Artificial intelligence
BFE	Binding free energy
VUM	Variants under monitoring

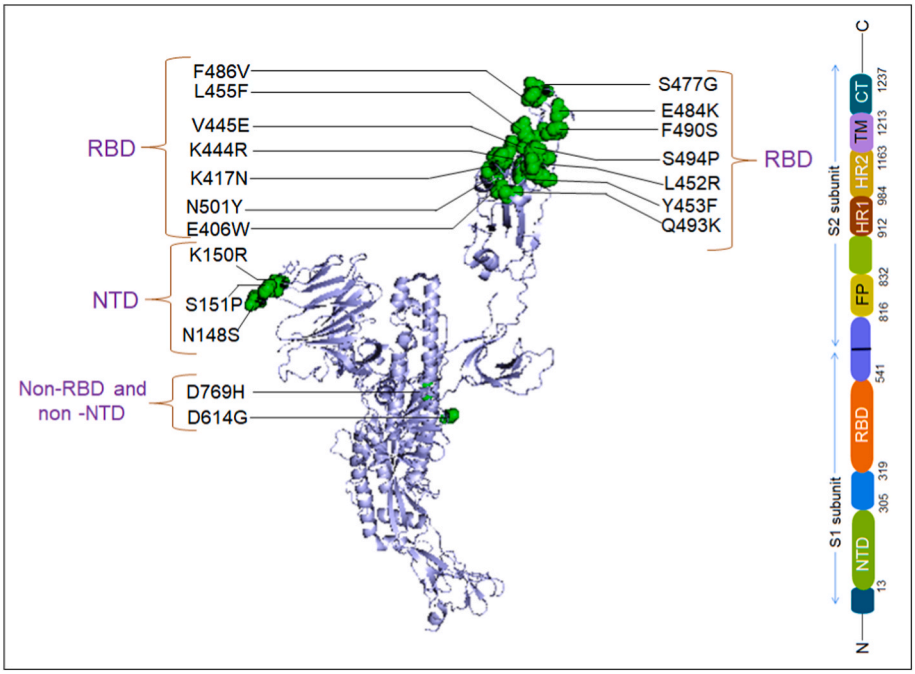

Fig. 1. Emerging mutations in SARS-CoV-2 are responsible for neutralizing antibodies (nAbs) escape and vaccine escape. These mutations should be considered to develop a mutation-proof, next-generation vaccine against pan-SARS-CoV-2 variants. For significant mutation selection, first, we listed all the mutations from all the SARS-CoV-2 variants (VOCs, VOIs, and VUMs), including Omicron and its emerging sublineages. From the list of mutations, we have selected vital mutations considering the frequencies and the characteristics of mutations (stability, molecular flexibility, etc.).

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