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.

VACUNAS. xxxx;xx(xx):xxx

Vacunas

www.elsevier.es/vac

Carta al Director

Multivalent vaccines against new SARS-CoV-2 hybrid variants

Dear Editor

On December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as causative agent of atypical pneumonia in Wuhan, China and by March 11 2020, the World Health Organization (WHO) announced that the disease caused by the SARS CoV2, COVID-19, had become a pandemic. According to available reports, more than 531 million cases were confirmed as well as 6.3 million deaths has been registered over the worldwide. Continuous evaluation and emergence of new SARS-CoV-2 variants followed by mixed-infections has become a serious global threat that causes new epidemic waves throughout the world.[1] Although vaccines developed to prevent SARS-CoV-2 infection are available, genetic recombination and spontaneous mutations in SARS-CoV-2 viral genome can lead to increase of pathogenicity, transmissibility, and immune evasion.[1]

Current available vaccines i.e. nucleic acid-based vaccines, viral vector based vaccines, subunit vaccines, and inactivated vaccines are established based on induction of strong immune responses against the spike (S) protein of SARS-CoV-2.[2] The surge of new SARS-CoV-2 variants harboring new mutations, particularly some variants presenting attractive mutations uniformly called variants of concerns (VOCs), have been considered as available spike protein for antigen based vaccines. The SARS-CoV-2 facilitates viral entry to host cell by the interaction between the spike (S) antigen and the binding domain of the angiotensin-converting enzyme 2 (ACE-2)[3]; However, the subsequent emergence of SARS-CoV-2 variants containing new mutations in the receptor binding domain (RBD) of spike protein are the main reasons for resistance to neutralizing antibodies, immune escape and low inefficacy of available vaccines to prevent infection.[4] Current evidences suggested that Omicron sub-lineages can easily recombine and fuse with each other in SARSCoV-2 cases of co-infection leading to a new phase of the SARS-CoV-2 pandemic. Thus, multivalent based vaccine can be an efficient approach for optimal vaccine development to combat with new SARSCoV-2 variants that mainly evolved in results of recombination between hybrid variants. The Moderna company recently developed new multivalent vaccine e.g. mRNA-1273.351 (targeting the B.1.351), or and mRNA-1273.351 (targeting B.1.351) to provide a broader range of protection against new SARS-CoV-2 variants.[5]

Multivalent vaccines could be providing more robust immune protection against SARS-CoV-2 novel variants due to 1) a much larger fraction containing essential all RBD epitopes, 2) much easier to be produced, 3) lower costs of production, and 4) more immunogenic.

For the first time, Xiang et al., 2020 showed the efficacy of Versatile, a multivalent cocktails nanoparticle against SARS-CoV-2 during in vitro examination.[6] According to recent Immunoinformatics studies, the multi-epitope peptide vaccine construct (MEPVC) has shown strong immune system induction with high binding affinity to TLR3.[1,4,7] Yu et al., 2022 were recognized the presence of 8 cytotoxic T lymphocyte epitopes, 17 helper T lymphocyte epitopes, 9 lineal B-cell epitopes, as well as 4 conformational B-cell epitopes within nucleotide sequence of SARS-CoV-2 virus strains.[1] Furthermore, Uttamrao et al., 2021 suggested several immune dominant epitopes of SARS-CoV-2 with suitable characteristics using unannotated open reading frames (uORFs).[4]

Regarding animal investigations, Chiba et al., 2021 recently developed nanoparticles which consist of multiple copies of the SARS-CoV-2 spike (S) protein covered with protein of the MS2 bacteriophages; this nanoparticle generated high neutralizing antibody titers in Syrian hamsters after a single immunization.[2] The MS2 bacteriophage is icosahedral virus that has been modified extensively for targeted delivery applications; Its capsid consists of a 27 nm with 32 pores that allows small molecules to diffuse out of the capsid. The MS2 viral capsid has been used for development of vaccines, delivery of very hydrophobic anticancer drug Taxol or imaging applications.[8] Guo et al., 2021 was also engineered

Please cite this article as: Ghazvini K y Keikha M. Multivalent vaccines against new SARS-CoV-2 hybrid variants. Vacunas. 2022. https://doi.org/10.1016/j.vacun.2022.06.002

a 197-amino-acid fragment of RBD conjugated with two carrier proteins that elicited robust neutralizing antibodies (nAbs) in immunized mice model after two doses.[9] Yuan et al., 2022 construct a bivalent multivalent vaccine based on the RBD sequence of D614G and B.1.351 that elicits induce robust immune responses against SARS-CoV-2 variants. The D614G/B.1.351 bivalent vaccine could protect mice in a prime-boost manner as well elicit robust nAbs response as third-dose booster in rhesus macaques.[3] Hunt et al., 2022 recently introduced multivalent designed proteins neutralize SARS-CoV-2 variants of concern (B.1.1.529, and B.1.617.2) with strong immune protection that administered with intranasal route in mice. It deals with two strategies for generating multivalent S protein binders from miniproteins, self-assembling homotrimers (TRI) and multidomain fusions (FUS).[10] these miniprotein receptors could be a broadly appropriate for antiviral therapeutic purpose particularly for VOCs with superior resistance to immune escape, high antigenic drift, and lower probabilities of autoimmune responses.

The global spread of SARS-CoV-2 in short span has intensified an urgent need for development of officious vaccines; several vaccine platforms have been introduced against COVID-19. However, additional vaccine platforms are under investigation to produce safer and more effective vaccine against newly emerged Omicron sub-lineages. Recently, nanoparticle-based vaccine as well as virus-like particle have shown robust immune response.[10,11] Nanoparticle-based vaccine used self-assembling scaffold constructions containing entire spike protein or receptor-binding domain of SARS-CoV-2 of various variants. On the other hand, virus-like particle vaccines are replication-defective viruses that stimulates immune response due to their microbial origin.[11] In summary, multivalent SARS-CoV-2 vaccine contains full set of RBD domain of various variants that highly capable to elicit a strong cross-reactive immune response against new SARS-CoV-2 variants.

Conflict of interest statement

There is no to declare.

REFERENCES

1. Yu M, Zhu Y, Li Y, Chen Z, Li Z, Wang J, et al. Design of a recombinant multivalent epitope vaccine based on SARS-CoV-2 and its variants in immunoinformatics approaches. Front Immunol. 2022;13, 884433.
2. Chiba S, Frey SJ, Halfmann PJ, Kuroda M, Maemura T, Yang JE, et al. Multivalent nanoparticle-based vaccines protect hamsters against SARSCoV-2 after a single immunization. Communications Biology. 2021;4(1):1–9.
3. Yuan Y, Zhang X, Chen R, Li Y, Wu B, Li R, et al. A bivalent nanoparticle vaccine exhibits potent cross-protection against the variants of SARS-CoV-2. Cell Rep. 2022;38(3), 110256.
4. Uttamrao PP, Sathyaseelan C, Patro LP, Rathinavelan T. Revelation of potent epitopes present in unannotated ORF antigens of SARS-CoV-2 for epitope-based polyvalent vaccine design using immunoinformatics approach. Front Immunol. 2021;12.
5. Li T, Huang T, Guo C, Wang A, Shi X, Mo X, et al. Genomic variation, origin tracing, and vaccine development of SARS-CoV-2: a systematic review. The Innovation. 2021;2(2), 100116.
6. Xiang Y, Nambulli S, Xiao Z, Liu H, Sang Z, Duprex WP, et al. Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2. Science. 2020;370(6523):1479–84.
7. Ismail S, Ahmad S, Azam SS. Immunoinformatics characterization of SARS-CoV-2 spike glycoprotein for prioritization of epitope based multivalent peptide vaccine. J Mol Liq. 2020;314, 113612.
8. Dedeo MT, Finley DT, Francis MB. Viral capsids as self-assembling templates for new materials. Prog Mol Biol Transl Sci. 2011;103:353–92.
9. Guo Y, He W, Mou H, Zhang L, Chang J, Peng S, Ojha A, et al. An engineered receptor-binding domain improves the immunogenicity of multivalent SARS-CoV-2 vaccines. mBio. 2021;12 (3). https://doi.org/10.1128/mBio.00930-21 e00930–21. PMID: 33975938; PMCID: PMC8262850.
10. Hunt AC, Case JB, Park YJ, Cao L, Wu K, Walls AC, et al. Multivalent designed proteins neutralize SARS-CoV-2 variants of concern and confer protection against infection in mice. Sci Transl Med. 2022;14(646) eabn1252.
11. Kim C, Kim JD, Seo SU. Nanoparticle and virus-like particle vaccine approaches against SARS-CoV-2. J Microbiol. 2022;60 (3):335–46.

Kiarash Ghazvini[a,b] y Masoud Keikha[a,b,*]

[a]*Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[b]*Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

**Corresponding author.*
E-mail address: keikham971@mums.ac.ir (M. Keikha).

https://doi.org/10.1016/j.vacun.2022.06.002
1576-9887/

Please cite this article as: Ghazvini K y Keikha M. Multivalent vaccines against new SARS-CoV-2 hybrid variants. Vacunas. 2022. https://doi.org/10.1016/j.vacun.2022.06.002