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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Combatting future variants of SARS-CoV-2 using an in-silico peptide vaccine approach by targeting the spike protein

Subhamoy Biswas\textsuperscript{a,}\textsuperscript{*}, Sumanta Dey\textsuperscript{b}, Shreyans Chatterjee\textsuperscript{b}, Ashesh Nandy\textsuperscript{b}

\textsuperscript{a} Department of Electrical Engineering, Jadavpur University, Kolkata, West Bengal, India
\textsuperscript{b} Centre for Interdisciplinary Research and Education, Kolkata, West Bengal, India

\section*{ARTICLE INFO}

\textbf{Keywords:}
In-silico drug design
SARS-CoV-2
Spike glycoprotein
Peptide vaccine
Computational model

\section*{ABSTRACT}

The far-reaching effects of the SARS-CoV-2 pandemic have crippled the progress of the world today. With the introduction of newer and newer mutated variants of the virus, it has become necessary to have a vaccine that remains useful against all the mutated strains of SARS-CoV-2. In this regard, peptide vaccines turn out to be a cheap alternative to the traditionally designed vaccines owing to their much quicker and computationally easier, and more robust design procedures. Here, in this article, we hypothesize that there are three possible peptide vaccine regions that can be targeted to prevent the surge of SARS-CoV-2. The candidates that were selected, were surface-exposed and were not sequestered by any neighbouring amino acids. They were also found to be capable of generating both B-cell and T-cell immune responses. Most importantly, none of them contains any spike protein mutation of the currently prevailing variants of SARS-CoV-2. From these findings, we have therefore concluded that these three regions can be used in wet labs for peptide vaccine design against the upcoming strains of SARS-CoV-2.

\section*{Introduction}

Since the inception of SARS-CoV-2 back in December 2019, according to WHO, there have been 211,730,035 reported cases of it with 4,430,697 deaths as of 23 August 2021 \cite{1}. With the introduction of various mutated strains of this virus that are even more virulent than their predecessors, methodical circulation of vaccines throughout the world has been a silver lining in this regard. mRNA vaccines like Pfizer BioNTech (BNT162b2) and Moderna (mRNA1273); adenovirus vector vaccines such as Oxford-AstraZeneca (Covishield), Sputnik V, Janssen, Convidicea, Sputnik Light; inactivated virus vaccines such as SinoPharm, CoronaVac, Covaxin; subunit vaccines such as EpiVacCorona, ZF2001, Abdala, Soberana 02 have granted emergency use around the world \cite{2,3}. Recent studies have shown that non-steroidal anti-inflammatory drugs (NSAIDS), particularly indomethacin can be a good option for initial therapeutic proceedings against COVID patients \cite{4}. Besides, the inactivation of the estrogen signaling pathway in lung cells \cite{5} might also help in damping the COVID-19 severity. Studies have also reflected the mechanisms behind natural and vaccine-induced immunity against SARS-COV-2 in humans \cite{6}, but the existence of long-term acquired immunity is under scrutiny \cite{7,8}.

Some mutated strains have been classified by the WHO as the Variants of Concern (VOC) on the basis of increased transmissibility, resistance towards vaccines and varied clinical symptoms. One of the deadliest strains of COVID-19 is the B.1.617.2 or Delta variant as it is more contagious (40–60% more transmissible than the B.1.1.7 or Alpha variant) \cite{9}. This strain was first documented in India around October 2020. It can break the vaccine cover quite easily. This strain can remain unaffected by a single dose of the Pfizer BioNTech vaccine \cite{10}. Even the effectiveness of the AstraZeneca ChAdOx1 nCoV-19 vaccine after the first dose was quite low for people affected by the Delta variant, but the effectiveness rose to 74.5\% (with a confidence interval of 95\%) after the second dose \cite{11}. Other SARS-CoV-2 Variants of Concern are the Beta strain (B.1.351, B.1.351.2, B.1.351.3) and the Gamma strain (P.1, P.1.1, P.1.2).

Some mutated strains of COVID-19 have altered amino acids in their Receptor Binding Domain (RBD) which can increase their binding affinity with the human ACE-2 receptor and hence, making them more infectious. A list of such of such variants and their corresponding alterations in the RBD domain is shown in Table 1. Thus, the question of long-term immunity against a variety of SARS-CoV-2 strains becomes the most important question that needs to be answered as soon as...
similar way, many promising peptide-based vaccines in COVID-19 are their applications against cancer-causing Human Papillomavirus (HPV) tremendous efficiency against multiple types of cancers, ranging from that takes into account the surface-exposed protein of SARS-CoV-2, that Pharma, DPX COVID-19 by IVM Inc, Ii-Key Peptide-based Covid-19 changes in the SARS-CoV-2 virus and can be easily modified to cope with those specific mutating strains by epitope recognition among conditions [15] and their stability can be easily obtained using standard large-scale production with low costs and high reproducibility [14]. peptide vaccines can respond rapidly as needed to various strains of the virus.

The spike protein has been chosen as the basis for this design as it is the antigenic component among all structural proteins for SARS-CoV-2 and it is responsible for inducing the host immune response. Vaccines designed from spike protein can induce protective immunity against viral infection [20].

The hypothesis

**Defining the problem**

The main focus of this in silico experiment will be to test whether our computational approach [19] is able to recommend the most suitable peptide vaccine targets against SARS-CoV-2 such that they evade all possible mutations in the frequently observed strains of concern of the virus and are not concealed by any neighbouring amino acids. The factors involved in evaluating this hypothesis include studying the mutation probability and solvent accessibility across the spike protein sequence and checking the epitope potential and autoimmunity of the selected peptide targets. The experiment’s outcome will be a list of peptide candidates based on which the vaccines can be prepared and checked for their efficacy in wet labs.

By determining mutation probability as an input parameter in this method, we ensure that the vaccine targets are based on only those regions of the spike protein which have shown negligible tendency to vary, both with time and among the host population.

**Mathematical foundation for the selection**

The first stage of the method involves a two-stepped model described as follows.

**Step 1: Defining a ‘w’ parameter to find conserved and exposed regions**

The process begins with calculating a w parameter for every possible 12-length peptide from the spike protein sequence. The w parameter depends on quantified representations of both surface exposure (ASA) and conservativeness (1/PV) for all these peptides. A ranking list for all the 12-length peptides is prepared in descending order of their w values. The top-ranked peptides are then “grouped” as per their position in the sequence, by following certain necessary conditions [19]. This eventually gave 16 grouped “peptide zones”.

**Step 2: Using 2D Polygon Representation, a mathematical model, to find peptide groups that are conserved, exposed and spanned across a large area**

This step deals with calculating a score for these zones with the help of a mathematical model, namely, “2D Polygon Representation” [19]. The model uses the normalized versions of three different parameters – average ASA, average 1/PV, and the span of each zone. Span gives the area that the peptide region covers on the surface of the protein. Average ASA or average 1/PV are defined as the average of the ASA and 1/PV values respectively of all the 12-length peptides that constitute the grouped peptide zone under consideration. In other words, average ASA and average 1/PV signify the overall surface exposure and the overall conservativeness respectively, of the peptide zone. The normalization of all the three parameters has been done on a common scale to indicate that each of the three parameters was of equal weightage. Fig. 1 shows the diagrammatic representation of the 2D Polygon model. The model represents them as the lengths of three concurrent arms, 120 degrees apart from each other. The area of the triangle formed by the three free ends of the arms is considered as the score generated by the model for that peptide zone. The zones are now ranked in descending order of their respective model scores. As in Fig. 1, OA, OB and OC represent the three arms and the area of AABC gives the score. Here |OA| = length of OA arm, gives the normalised average ASA. Similarly, |OB| gives normalised average 1/PV and |OC| gives the normalised length of the peptide region.

### Table 1

List of some of commonly observed mutated strains of SARS-CoV-2 and their mutation in the receptor binding domain.

| Commonly observed variants | Pango Lineage | Mutations in the receptor binding domain (RRD) in the surface glycoprotein |
|----------------------------|--------------|-------------------------------------------------------------------------|
| Alpha                      | B.1.1.7      | E484K, S494P, N501Y                                                     |
| beta                       | B.1.351      | K417N, E484K, N501Y                                                     |
| Gamma                      | P.1, P.1.1, P.1.2 | K417N, E484K, N501Y                                                     |
| Delta                      | B.1.617.2, AY.1, AY.2, AY.3 | K417N, L452K, T478K                                                     |
| Omicron                    | B.1.1.5.29   | G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484K, Q493R, G496S, Q498R, N501Y, Y505H |
| Lambda                     | C.37         | L452Q, F490S                                                           |
| Mu                         | B.1.621      | R346K, E484K, N501Y                                                     |
| Kappa                      | B.1.617.1    | L452R, E484Q                                                           |
| Eta                        | B.1.525      | E484K                                                                 |
| Iota                       | B.1.526      | L452R, S477N, E484K                                                     |
| Epsilon                    | B.1.427, B.1.429 | L452R                                                               |
| Zeta                       | P.2          | E484K                                                                 |
| -                          | B.1.1.519    | T478K                                                                 |
| -                          | B.1.620      | S477N, E484K                                                           |
| -                          | B.1.177      | T445C                                                                 |
| -                          | B.1.617.3    | L452R, E484Q                                                          |
The spike protein sequence for our study have been retrieved from the NCBI database [29]. We have particularly used the sequence YP_009724390.1 as input for the ABCpred server for determining the B-cell epitopes [30]. The SABLE server [31–34] has been used to obtain the solvent accessibility values for each amino acid position of the spike protein sequence. Using the moving average technique with a window of 12, the quantified expressions of surface exposure (ASA) of the 12-length peptides are then obtained.

Fig. 2 gives a flowchart of the entire protocol of designing vaccine candidates for SARS-CoV-2. Hence, by executing all the aforementioned steps in this approach, we hypothesize that this will give us the regions on the surface glycoprotein of SARS-CoV-2 that should be targeted for designing effective vaccines.

Data sources

The spike protein sequences for our study have been retrieved from the NCBI database [29]. We have particularly used the sequence YP_009724390.1 as input for the ABCpred server for determining the B-cell epitopes [30]. The SABLE server [31–34] has been used to obtain the solvent accessibility values for each amino acid position of the spike protein sequence. Using the moving average technique with a window of 12, the quantified expressions of surface exposure (ASA) of the 12-length peptides are then obtained.

Fig. 2 gives a flowchart of the entire protocol of designing vaccine candidates for SARS-CoV-2. Hence, by executing all the aforementioned steps in this approach, we hypothesize that this will give us the regions on the surface glycoprotein of SARS-CoV-2 that should be targeted for designing effective vaccines.

Evaluation of the hypothesis

With the help of the two-stepped mathematical approach (\( w \) parameter and 2D Polygon Representation), peptide regions were selected which were surface accessible, conserved and spanned across a broad area [19]. The ones which lacked insufficient T-cell immunogenicity and showed significant chances of auto-immunity were discarded thereafter. Table 2 gives the list of the remaining peptide regions which were shortlisted as possible vaccine candidates.

Now, using PyMOL, we have visualised these 4 peptide regions. The 3D model “6VYB” was first loaded in the software before highlighting these peptide regions. Fig. 3(A)–(D) show an overview of the vaccine targets on the 3D simulation in PyMOL.

As in Fig. 3(A)–(D), the regions 527–541, 459–470 and 987–1001 are very well surface-exposed. On the contrary, the region 1021–1035 is almost fully covered by its neighbouring amino acids, and hence, not accessible even after having a high normalized average ASA. A possible explanation for this is that the spike protein has a trimeric structure, that is, it consists of three chains A, B and C. Our analyses are limited only to the protein sequence of a single chain. Because the region 1021–1035 falls in the place where the three chains converge together, it gets enclosed within the junction area of the chains and as a whole, it is not well accessible. Ultimately, we are left with three peptide candidates: 527–541, 459–470 and 987–1001, which can be tested further. Region 1021–1035, meanwhile, has to be discarded.

Using the ABCpred server, we have then checked the B-cell immunogenicity of the three regions tentatively selected. We have used a threshold of 0.65 for a stricter condition of predicting the B-cell epitopes. We looked for all possible 16-length B-cell epitopes from the server using that threshold, as listed in Table S1 of the Supplementary file. The corresponding score given beside each entry in Table S1 in the file represents the probability of such a peptide being a B-cell epitope. A higher score means a greater probability of that happening. Now, on comparing the three regions 527–541, 459–470 and 987–1001 with this...
Fig. 2. Complete overview of our approach to design peptide vaccine targets for COVID-19.
list, we found that all of them were contained partially or fully with the matching epitopes. This shows that these regions not only can cause a T-cell immune response but can also generate a B-cell response. Table 3 gives a list of the best matching B-cell epitope with the best possible score corresponding to the three peptide regions.

In the end, we retrieved the information about the mutations in the variants of concern and variants of interest of SARS-CoV-2 (as of August 18, 2021). In Table 4, for each variant of concern and each variant of interest, we have compared the three regions with the spike protein mutations associated with the variant. For every case, we found that there were no matches. We further compared the regions with the mutations occurring in the spike protein of the currently surging Omicron variant of SARS-CoV-2 [28], and observed that for this case as well, there was no coherence between the mutations and the peptide targets.

Therefore, we can comment that the 3 regions, PKKSTNLVKNKCVNF (527–541), SNLKPFERDIST (459–470) and VEAEVQIDRLITGRL (987–1001) have the following characteristics as listed below:

3.1 They are surface-accessible, conserved and occupy a broad area on the spike protein surface.
3.2 They show both B-cell and T-cell immunogenicity.
3.3 They have negligible chances of causing any autoimmune threats in a human host.
3.4 Among the significant variants of SARS-CoV-2 in the current standpoint, there is no such mutation that falls within our proposed peptide vaccine candidates.

Taking all the above characteristics into account, we can therefore suggest that these peptide regions are suitable for vaccine design against SARS-CoV-2. A special significance of the region SNLKPFERDIST (459–470) is that it is a highly surface-accessible and a highly conserved peptide region falling under the receptor-binding domain (RBD) of the spike protein, that is, the region where it binds with the ACE2 receptor which ranges from 318 to 513 amino acid residues [35]. Moreover, the

Table 2

| Starting position of the candidate in the sequence | Ending position of the candidate in the sequence | Peptide stretch |
|---------------------------------------------------|-----------------------------------------------|----------------|
| 1021                                              | 1035                                          | SANLAATKMSECVLG |
| 527                                               | 541                                           | PKKSTNLVKNKCVNF |
| 459                                               | 470                                           | SNLKPFERDIST   |
| 987                                               | 1001                                          | VEAEVQIDRLITGRL |

Table 3

| Peptide regions   | B-cell epitope     | Start position | End position | Score |
|-------------------|--------------------|----------------|--------------|-------|
| PKKSTNLVKNKCVNF   | CGPKKSTNLVKNKCVNF  | 525            | 540          | 0.86  |
| VEAEVQIDRLITGRL   | EEAEVQIDRLITGRLQS  | 988            | 1003         | 0.73  |
| SNLKPFERDIST      | RSENLKPFERDISTEI   | 457            | 472          | 0.65  |

Fig. 3. A brief overview of the geometrical location of the four target regions (A) 459–470, (B) 527–541, (C) 987–1001 and (D) 1021–1035, on the 3D model of the trimeric structure of spike protein. The target regions have been highlighted in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The RBD region is a critical target for neutralizing antibodies and some vaccines [36]. Now as we are able to find the region, SNLKPFERDIST (459–470) which completely lies within this RBD domain, the peptide vaccine designed using this amino acid stretch can indeed be a suitable candidate for a potential therapeutic. Additionally, as this peptide region is highly conserved throughout the various strains, we can hypothesize that it plays a critical role in attaching with the human ACE2 receptor directly or indirectly.

However, these peptides when used alone, generally show low immunogenicity. The targets can be, thus, coupled with innate immune agonists in the form of adjuvants to improve the immunogenic response and ensure a long-term immunity in the host body [37]. Furthermore, in vitro and in vivo evaluation of such a vaccine on animal models through wet lab tests is also needed to verify its efficacy before performing its trial on the infected patients.

### Table 4
Comparison of the three peptide vaccine candidates with the mutations present in the most significant variants of SARS-CoV-2. The table shows that the regions are all free from any of the listed mutations.

| For variants of concern | Variant | Spike Protein mutations | Peptide Sequences to be matched | Remark |
|-------------------------|---------|-------------------------|-------------------------------|--------|
| Alpha (B.1.1.7)         | Originated in: United Kingdom | 69del, 70del, 144del, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Beta (B.1.351.2, B.1.351.3) | Originated in: South Africa | D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Delta (B.1.617.2, AY.1, AY.2, AY.3) | Originated in: India | T19R, V70F, T95I, G142D, E156-, F157-, R158G, A222V, W258L, K417N, L452R, T478K, D614G, P681R, D950N | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Gamma (P.1, P.1.1, P.1.2) | Originated in: Japan, Brazil | L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| For variants of interest | B.1.427 | Originated in: United States (California) | L452R, D614G | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| B.1.429 | Originated in: United States (California) | S13I, W152C, L452R, D614G | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Eta (B.1.525) | Originated in: United Kingdom, Nigeria | A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Iota (B.1.526) | Originated in: United States (New York) | L5F, D80G, T95I, Y144-, F157S, D253G, L452R, S477N, E484K, D614G, A701V, T859N, D950H, Q957R | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| Kappa (B.1.617.1) | Originated in: India | T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |
| B.1.617.3 | Originated in: India | T19R, G142D, L452R, E484Q, D614G, P681R, D950N | PKKSTNLVKNNKCVNF (527-541), SNLKPFERDIST (459-470), VEAEVQIDRLITGRL (987-1001) | No matches found |

### Discussion
The findings described here takes a step ahead from our previous work [19] to propose target regions on the spike protein that can be utilised for vaccine design against the most impactful strains of SARS-CoV-2 prevailing right now. Moreover, from the structural analysis of the spike protein explained in this article, we have found that one particular peptide region, mentioned in the previous work, remains sequestered by its neighbouring amino acids, for which it has not been recommended for use.

The three remaining peptide candidates which we highly recommend for vaccine production are conserved that is, they have not been affected by any sort of mutations in these variants. Simultaneously, these three regions are also well exposed on the surface of the spike protein, have negligible chance of causing autoimmune disorders, and are capable of producing adequate B-cell and T-cell epitopes in the host.
However, our approach is limited to an in silico study. Therefore, through different phases of human trials, it is yet to be seen whether vaccines prepared using these targets can sustain a prolonged immunity in the human host. Safety is another area of concern when it comes to choosing the proper adjuvants for this design.

Nevertheless, the protocol suggests that the peptide vaccines prepared using these regions have a high possibility of preventing outbreaks if used in response to the introduction of a new strain of the virus as well as work efficiently against the existing strains. They can be universally used as a proactive safeguard against SARS-CoV-2 by mitigating the risk of its re-emergence in humans. With these peptides, or by adopting the approach communicated in this article, perhaps we can also prevent a “SARS-CoV-3” in the future, that is, this technique can also be followed up to prevent future pandemics.

It is now up to the wet lab scientists to use these peptide stretches and combine them with suitable adjuvants to design effective peptide vaccine formulations. We envision that with this procedure, the recurring outbreaks of the COVID 19 strains can be reduced while minimising the massive economic losses as well.

Funding source
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Ethical approval
Not required.

CRediT authorship contribution statement
Subhamoy Biswas: Methodology, Formal analysis, Software, Visualization, Resources, Data curation, Writing – original draft. Sumanta Dey: Visualization, Resources, Formal analysis, Validation, Writing – original draft. Shreyans Chatterjee: Resources, Formal analysis, Writing – original draft. Ashesh Nandy: Supervision, Project administration, Validation, Writing – review & editing.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements
We would like to thank Professor Subhash C. Basak (Department of Chemistry and Biochemistry, University of Minnesota Duluth, Minnesota, US) for his constant support during the preparation of the work reported in this paper.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2022.110810.

References
[1] World Health Organization. WHO Coronavirus (COVID 19) Dashboard. [accessed on 2021 August 23] http://coronavirus.who.int/.
[2] Wikipedia contributors. COVID-19 vaccine. Wikipedia, The Free Encyclopaedia. [accessed on 2021 August 12] https://en.wikipedia.org/wiki/Covid-19_vaccine.
[3] World Health Organization. WHO lists additional COVID-19 vaccine for emergency use and issues interim policy recommendations, 2021 May 7 [accessed on 2021 August 12] https://www.who.int/news/item/07-05-2021-who-lists-additional-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations.
[4] Oh KK, Adnan M, Cho DH. Drug-repurposing against COVID-19 by targeting a key signaling pathway: An in silico study. Medical Hypotheses, Volume 155, 2021, 110656, ISSN 0306-9877, doi: 10.1016/j.mehy.2021.110656.
[5] Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol 2021;21(8):475-84. https://doi.org/10.1038/s41577-021-00782-2.
[6] Dan JM, Matren J, Kate Yu, Hastie KM, Yu BD, Falike E, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 2021;371(6529).
[7] Gaebler C, Wang Z, Lorenzi JCC, Mueckl F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. Nature 2021;591(783)S:339-44. https://doi.org/10.1038/s41586-021-03207-w.
[8] Hagen A. How Dangerous Is the Delta Variant (B.1.617.2)? [Blog]. American Society for Microbiology. 2021 July 30 [accessed on 2021 August 12]; https://amss.org/Articles/2021/July/How-Dangerous-is-the-Delta-Variant-B-1-617-2.
[9] Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. Nature Medicine 2021;28(7):276-80. https://doi.org/10.1038/s41591-021-00779-9.
[10] Lopez Bernal J, Andrews M, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. N Engl J Med 2021;385(7):585-94. https://doi.org/10.1056/NEJNoa2108991.
[11] Skwarczynski M, Toth I. Peptide-based synthetic vaccines. Chem Sci 2016;7(2):842-54. https://doi.org/10.1039/c5sc03892h. PMID: 28791171; PMCID: PMC5529997.
[12] Li W, Joshi M, Singhania S, Ramsey K, Murphy A. Peptide vaccine: progress and challenges. Vaccines 2014;3(2):515-36. https://doi.org/10.3390/vaccines2030315.
[13] Dey S, De A, Nandy A. Rational design of peptide vaccines against multiple types of human papillomavirus. Cancer 2016;115:1.S1.https://doi.org/10.4137/CIN.2016.1.1.
[14] Skwarczynski M, Toth I. Peptide-based synthetic vaccines. Chem Sci 2016;7(2):842-54. https://doi.org/10.1039/c5sc03892h. PMID: 28791171; PMCID: PMC5529997.
[15] Li W, Joshi M, Singhania S, Ramsey K, Murphy A. Peptide vaccine: progress and challenges. Vaccines 2014;3(2):515-36. https://doi.org/10.3390/vaccines2030315.
[16] Dey S, De A, Nandy A. Rational design of peptide vaccines against multiple types of human papillomavirus. Cancer 2016;115:1.S1.https://doi.org/10.4137/CIN.2016.1.1.
[17] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT00094653, MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Unresectable or Metastatic Melanoma; 2011 June 23 [cited 2022 Jan 06]. Available from: https://c

Medical Hypotheses 161 (2022) 110810
8

[33] Wagner M, Adamczak R, Porollo A, Meller J. Linear regression models for solvent accessibility prediction in proteins. J Comput Biol 2005;12(3):355–69. https://doi.org/10.1089/cmb.2005.12.355.

[34] Porollo A, Adamczak R, Wagner M, Meller J. Maximum Feasibility Approach for Consensus Classifiers: Applications to Protein Structure Prediction, CIRAS 2003 (conference proceedings).

[35] Di Paola L, Hadi-Alijanvand H, Song X, Hu G, Giuliani A. The discovery of a putative allosteric site in the SARS-CoV-2 spike protein using an integrated structural/dynamic approach. J Proteome Res 2020;19(11):4576–86. https://doi.org/10.1021/acs.jproteome.0c00273.

[36] Min L, Sun Q. Antibodies and vaccines target RBD of SARS-CoV-2. Front Mol Biosci 2021;8:247. https://doi.org/10.3389/fmolb.2021.671633.

[37] Long Y, Sun J, Liu T, Tang F, Zhang X, Qin Q, et al. CoVac501, a self-adjuvanting peptide vaccine conjugated with TLR7 agonists, against SARS-CoV-2 induces protective immunity. bioRxiv 2021. https://doi.org/10.1101/2021.04.10.439275.