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In silico comparative study of SARS-CoV-2 proteins and antigenic proteins in BCG, OPV, MMR and other vaccines: evidence of possible putative protective effect

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Abstract

Background:

Coronavirus Disease 19 (COVID-19) is a viral pandemic disease that induces severe pneumonia in human. Until now, no effective therapeutic interventions or specific vaccines have been developed. In this paper, we attempt to investigate the putative implication of 12 vaccines, including BCG, OPV and MMR in the protection against COVID-19. First, we compared sequences of the main antigenic proteins in the investigated vaccines and SARS-CoV-2 proteins. Then, we investigated identified segments using a combination of structural and antigenicity prediction tools to assess their immunogenic effect.

Results:

A total of 14 highly similar segments were identified in investigated vaccines. After mapping on S and N proteins and analysis of the antigenicity prediction, three segments, in Hepatitis B, Tetanus and Measles proteins showed structural and antigenic properties that can induce possible putative protective effect.

Conclusions:

HBV, Tetanus and Measles vaccines should constitute a good candidate for a clinical trial to evaluate their real protective effect against COVID-19.

Background

Since December 2019, an emerging virus has been spreading worldwide, causing a huge health and economic crisis which is expected to continue for a prolonged period. The new discovered coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for the Coronavirus disease (COVID-19), caused a worldwide pandemic, declared by the World Health Organization (WHO) in March 2020 [1]. So far, SARS-CoV-2 has been responsible for more than a million fatalities and more than 41 million confirmed cases (from December 8, 2019 to October 21, 2020) [2].

SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus. It belongs to the family of *Coronaviridae,* the subfamily of O*rthocoronavirinae* and the genus Betacoronavirus [3]. The viral genome of approximately 29903 nucleotides, contains 5'and 3' untranslated regions and eleven Open Reading Frames (ORF) encoding eleven proteins including the Spike (S) and the Nucleocapsid (N) proteins identified as the main antigenic proteins [4, 5].

The total number of SARS-CoV-2 infected persons and death cases varied from one country to another. In the majority of cases, important health issues were reported, such as in US, Brazil, India and Russia causing respectively, 218 131, 153 905, 115 197 and 24 366 deaths and 8 065 615, 5 235 344, 7 597 063, 1 415 316 confirmed cases up to 18 October 2020 [6]. However, in other regions, such as Madagascar, Sierra Leone, Nicaragua and Uruguay the number of cases seems to be limited. The number of deaths did not exceed 300 up to the same date [6]. These fluctuations can be explained by different factors, such as health infrastructure, mitigation strategy and also cultural behavior [7]. It was also attributed to the vaccination strategies used in those regions. Indeed, it was previously demonstrated that administration of vaccines including attenuated viruses such as OPV (Oral Poliovirus Vaccine), MMR (Measles, Mumps and Rubella vaccines) and BCG (Bacillus Calmette-Guérin) vaccines could improve innate immune response to fight different pathogens. Furthermore, it was suggested that adoption of a universal and long-standing BCG policy in those countries might have a protective effect against COVID-19 [7]. Nevertheless, no comprehensive fundamental evidence showed the relationship between regular vaccination and the acquisition of immunity to SARS-CoV-2 until now. Indeed, a recent epidemiological study, based on a large cohort demonstrated no links between the administration of BCG vaccine and COVID-19 virulence [8] while at the same time, after refining the epidemiological study, a strong correlation was reported [9]. The protective potential of MMR vaccine was also investigated based on bioinformatic analysis of the S protein. However, no similarity with the crystal structure of S protein has been reported [10]. Nevertheless, the use of existing vaccines is of great interest and can help mitigation of the COVID-19 pandemics.

In this paper, we attempt to investigate the putative implication of attenuated vaccines (BCG, OPV and MMR) and nine other vaccines. We aim to identify amino-acid regions in all SARS-CoV-2 proteins similar to main antigenic proteins in other vaccines which may lead to the production of cross-reactive antibodies against the target agent and SARS-CoV-2 and/or the induction of cellular immunity. To achieve this goal, we used a combination of bioinformatic tools to compare the amino-acid sequences of the main antigenic protein of investigated vaccines and all SARS-CoV-2 proteins as well as to predict immunogenicity of similar identified patterns.

Results

Amino acid sequence alignment and hot spot analysis

The global amino acid identity between the main antigenic protein of investigated vaccines and SARS-CoV-2 proteins does not exceed 63%. For structural proteins, it varied between 21% and 55% (identity levels for the Spike and Matrix proteins respectively with the Polyprotein E1/E2 of Rubella virus and the HAV VP1 protein). For non-structural proteins, identity levels varied between 21 and 63% (identity rates of ORF1a and ORF3a proteins respectively with HBsAg-adr protein of Hepatitis B virus and Tetanus Toxin protein) (Additional material 1).

Similar segments with main vaccine antigenic protein were identified all along structural and non-structural proteins of SARS-CoV-2. The majority were shorter than five consecutive amino-acids for all SARS-CoV-2 proteins (Additional material 2-13). Nevertheless, a total of twelve patterns of six to eight similar consecutive amino-acids were identified in comparison against main antigenic proteins in: Poliovirus, Measles, *Streptococcus pneumoniae*, Tetanus, Mumps, Hepatitis B, Hib and BCG vaccines (Table1). Two similar segments were identified through comparison of Poliovirus, Measles, PCV10 and Hib proteins and SARS-CoV-2 structural proteins (S and N) and also non-structural proteins (ORF 1a, ORF 6 and ORF 8). While, tetanus, Mumps, Hepatitis B and BCG antigenic proteins showed no more than one similar segment with SARS-CoV-2 proteins (Table1). Among described peptides, seven were similar to others in S protein, obtained with antigenic proteins in poliovirus Sabin 3, *S pneumoniae*, tetanus, Mumps, Hepatitis B and Hib vaccines. The patterns length varied between six and seven amino acids. Also, one peptide of eight amino acids (GTSPARMA) detected in the Poliovirus VP1 sequence matched with the N protein of the SARS-CoV-2.

We also identified two discontinuous patterns of 10 amino-acids (DISGFNSSVI, MSLSLLDLYL) in the tetanus toxin and the hemagglutinin measles proteins which present 90% and 80% similarity with another segments (DISGINASVV, IELSLIDFYL) in the S and ORF7b proteins of SARS-CoV-2 respectively.

Table1: Description of similar patterns of more than five amino-acids obtained in vaccine antigenic proteins and SARS-CoV-2 proteins

Vaccine	N° of similar segment	Vaccine protein			SARS-CoV-2 Protein		
		Designation	Segment	Position	Designation	Segment	Position
Poliovirus	2	VP1 protein (Sabin 1)	GTAPARIS	188-195	N	GTSPARMA	203-211
		VP1 protein (Sabin 3)	LDPLSE	289-295	S	LDPLSE	293-299
Measles	2	Fusion protein	QECLRG	359-364	ORF6	QECVRG	21-27
			IQVGSRR	433-440	ORF8	IRVGARK	47-54
Streptoccocus pneumonea	2	Capsular polysaccharide biosynthesis protein (serotype19F, 18C, 14, 7, 4, 1)	IGFLAGVI	182-190	S	LGFIAGLI	1218-1226
		Capsular polysaccharide biosynthesis protein (serotype19F, 18C, 14, 5)	SSVAFA	33-39	S	NSVAYS	703-708
Hib	2	Capsular polysaccharide biosynthesis protein	KNINDS	210-215	S	KNLNES	1191-1196
			FILNKKI	73-79	ORF1a	FLLNKEM	3183-3189
BCG	1	Immunogenic protein MPB64	IFMLVT	5-11	E	VFLLVT	25-31
Tetanus	1	Toxin protein	NILMQY	84-90	S	NLLLQY	751-756
Mumps	1	Fusion protein	DISTEL	448-454	S	DISTEI	467-473
Hepatitis B	1	HBs Ag-adr	PGTSTTS	111-117	S	PGTNTSN	600-606

Immunogenicity prediction

Our analysis has been conducted in two inspections. First, we focused on characterizing the immunogenicity of the matching sequences with S and N proteins for their involvement in modulating the immune response of the host [11, 12].

Regarding the pattern identified in N protein, no significant similarity was obtained with the crystal structure of the corresponding protein. Among the seven patterns identified in S protein, four segments (LDPLSE, NSVAYS, NLLLQY, PGTNTSN) respectively from Polio, PCV10, Tetanus and HBV vaccines have been mapped to the structure of the spike protein (figure 1A). The three other patterns (LGFIAGLI, KNLNE and DISTEI) were not solved by the electron density map from the Cryo-EM structure. Among the four retained

patterns, except for the segments PGTNTSN and LGFIAGLI, none of the other peptides showed a putative interaction with one of the MHC receptors predicted by IEDB analysis resource NetMHCpan. However, the prediction for both of these peptides showed a weak peptide score of 0.07 and 0.02 respectively (0 indicates no MHC capacity, and 1 indicates a high probability). The segment PGTNTSN, present in the Hbs Ag of Hepatitis B virus adr strain, was located in a turn region and showed the highest level of exposure to the solvent (figure 1 B) with an average SASA value of 407 $Å^2$. Thus, among the seven candidate segments, only PGTNTSN showed a putative humoral immunogenicity predicted by EpiJen ranked as the fourth best match with a predicted IC50 Value of 4.33. (Figure 1 C)

In the second examination, we focused on a list of hits that belonged to any of the investigated vaccine sequences and that matched any of the other proteins of SARS-CoV-2. All the patterns have been explored for their antigenic potential using EpiJen and IEDB NetMHCpan methods. They did not show any putative antigenicity properties predicted by the servers.

Discontinuous patterns with more than ten residues were discarded from the analysis as they showed low levels of similarity. Nevertheless, we have retained two segments in Tetanus toxin protein (DISGFNSSV) and chain A, hemagglutinin Protein of the measles virus (MSLSLLDLYL) that significantly matched with SARS-CoV-2 Spike and ORF7b proteins. The segment DISGINASVV of the S protein that matched the sequence DISGFNSSVI of the tetanus toxin showed a putative interaction with one of the MHC receptors predicted by IEDB analysis resource NetMHCpan. These two matching sequences showed high peptide scores of 0.88 and 0.76 (0 indicates no MHC capacity, and 1 indicates a high probability) respectively for SARS-CoV-2 S protein of and the tetanus toxin protein. Regarding segments ORF7b and Measles hemagglutinin Protein, both overlap significantly with regions of putative T-cell antigenicity. That identified segment corresponded to a random coil segment (MSLS) spanned by an alpha helix of six residues (LLDLYL) in the crystal structure of the hemagglutinin [13]. The segment also interacted with a large pocket formed mainly by four strands of a beta-sheet containing many aromatic amino acids. The pocket was similar to the grooves of the MHC I and MHC II molecules (Figure 2).

Discussion

In this study, we investigated the potential protective effects against COVID-19 induced by existing vaccines. The use of existing vaccines could help mitigation of the COVID-19 pandemics very quickly with a safe and validated vaccine while waiting for the development of specific vaccines or preventive therapies. To achieve this goal, we used a combination of amino acid alignments, structural and antigenicity prediction tools to evaluate main antigenic proteins in twelve commonly used vaccines including BCG, OPV and MMR vaccines.

In our study, hotspot analysis demonstrated that main detected patterns were shorter than five amino acids and therefore could not constitute a putative T-cell epitope. Nevertheless, twelve patterns of six to eight amino-acids were investigated. After mapping on S protein and analyzing of the antigenicity prediction, only the pattern ‘PGTNTSN’ detected in HBsAg of Hepatitis B virus corresponded to an exposed site in S protein and showed the highest values of accessible surface area. Thus, its structural properties were consistent with its putative neutralizing capacity. Naturally, the antibodies would be able to recognize the targeted epitope on the whole assembled structure of the virus and therefore, the epitope must be accessible at the surface of the spike protein. On the other hand, in their recent attempt to establish the antigenicity map of SARS-CoV-2, Zhang et al (2020) [12] have noticed that a segment called IDh spanning residues 522–646 was found to induce a positive reaction by B-cells from sera of convalescent COVID-19 patients. The pattern ‘PGTNTSN’ was included in the IDh epitope and we were able to identify strong prediction metrics using the EpiJen server. Thus, the induced immunological reaction by this segment would be humoral response. Furthermore, our results were in agreement with the work achieved by Tajiri et al (2010) [14]. The authors showed that two regions of HBsAg (residues 104-123 and 108-123) containing the epitope matching the ‘PGTNTSN’ segment of SARS-CoV-2 were capable of binding two human monoclonal antibodies which highlighted the immunogenic capability of these segments. Nevertheless, only, randomized controlled trials might provide evidence of induced protective effect against COVID-19. In many countries, the HBV vaccine is commonly recommended or mandatory for healthcare and wet lab workers. It is therefore worth it investigating the relationship between the prevalence of SARS-CoV-2 and HBV vaccination.

Interestingly, our analysis showed the presence of two segments of ten amino acids from the Tetanus toxin protein and chain A of the Measles hemagglutinin Protein, similar to other located in the S and ORF7b proteins. The segment ‘DISGINASV’, matching with the toxin tetanus protein has been described previously to be part of an antigenic peptide in the S protein of SARS-CoV [15]. Regarding the segment matching with the ORF7b protein, which may have. an accessory function whose role is yet to be determined [16], we could not exclude its possible immunogenic role. On the other hand, we have also recorded significant global identity level between Measles fusion and hemagglutinin proteins and SARS-CoV-2 spike, envelope and matrix proteins (45-50%) (suppl mat. 1). Furthermore, another

study using other Measles and Rubella sequences except those from Measles and Rubella vaccine strains (Edmonston Measles and Rubella Wistar RA 27/3 strains) revealed similarity between the N terminal region of SARS-COV-2 Spike protein and the Fusion protein of Measles virus as well as the envelope protein of Rubella virus. Nevertheless, no similarity was obtained with the crystal structure [10]. The Measles vaccine is an attenuated vaccine administered as part of MR (Measles and Rubella) or MMR (Measles, Mumps and Rubella). It was previously demonstrated that attenuated vaccines such as OPV, BCG and MMR could improve the innate immune response to other pathogens [17]. These non-specific effects of live vaccines involved the trained immunity which refers to the memory-like characteristics of innate immune cells [18]. Indeed, following exposure to a primary stimulus like a vaccine or a microbial component, innate immune cells, especially monocytes and NK-cells, undergo epigenetic reprogramming that subsequently regulate cytokine production and cell metabolism and collectively enhance responsiveness to an unrelated secondary stimulus. In this line, observational studies reported a decrease in hospitalization rate and overall mortality among immunized children with live attenuated vaccines [19]. Furthermore, pediatric populations seem to be protected against COVID-19, especially in low and middle incomes countries. The long-term use of attenuated vaccine, with high coverage, could explain the low symptomatic infection rate among children. Thus, MMR vaccine might also constitute a good candidate for a clinical trial to assess its real protective effect against COVID-19.

Conclusions

The control of COVID-19 will be possible only after a large immunization of the world population through herd immunity or vaccination. Nevertheless, conception, validation and mass production of an effective and safe vaccine is difficult to achieve. Thus, the use of existing vaccines might help mitigation of the COVID-19 pandemics very quickly. This study demonstrated a possible putative protective effect of HBV, Tetanus and Measles vaccines against SARS-CoV-2 which should be confirmed by randomized controlled trials. Thus, HBV, Tetanus and Measles vaccines should constitute a good candidate for a clinical trial to evaluate their real protective effect against COVID-19.

Materials And Methods

Investigated Vaccines and Sequences

Our study focused on twelve vaccines including attenuated vaccines (BCG, OPV, MMR vaccines) and inactivated ones (Tetanus, *Corynebacterium diphtheriae, Bordetella pertissus,* Hepatitis B, Hepatitis A, *Haemophilus influenzae type B* (Hib) and *Streptococcus pneumoniae* vaccines (PCV10) (Table 2).

The full amino-acid sequences of main antigenic proteins (n=30) corresponding to the 12 investigated vaccines were obtained from NCBI Genbank database. Accession numbers are listed in Table 1. In addition, the amino-acid sequences of the structural proteins (Spike (S), Envelope (E), Matrice (M), Nucleocapsid (N) and non-structural proteins (ORF1ab, ORF1a, ORF3a, ORF6, ORF7a, ORF7ab, ORF8 and ORF10) of SARS-CoV-2 Wuhan reference strain (NC_045512) were obtained.

Table 2: vaccines and corresponding antigenic proteins investigated in this study

Vaccine	Protein	Accession N°	Reference
Tetanus	Toxin protein	AAA23282.1	24
Corynebacterium diphtheriae	Toxin protein	CAA00374.1	24
Hepatitis B	HBsAg-adw2	AAW65557.1	25
	HBsAg-adr	AAW65588.1	
Bordetella pertussis	Toxin protein	AQW64178.1	24
Measles	Hemagglutinin protein	AAF85705.1	
	Fusion protein	AAF85704.1	26
Rubella	Polyprotein E1/E2	ACN50046.1	26
Mumps	Fusion protein	ACN50030.1	
	Hemagglutinin/neuraminidase protein	ACN50032.1	26
Hepatitis A	VP1 protein	AAA45466.1	
	VP3 protein	AAA45466.1	27, 28
Bacillus Calmette-Guérin (BCG)	Immunogenic protein MPB83	BAA11027.1	
	Immunogenic protein MPB70	BAA07402.1	29-31
	Immunogenic protein MPB64	AIC33023.1	
Hemophilus influenzae serotype B (Hib)	Capsulation protein	CWW30252.1	24
	Capsular polysaccharide biosynthesis protein	WP_015702013.1	
Poliovirus	VP1 protein (Sabin 1 strain)	AAL89597.1	32
	VP1 protein (Sabin 2 strain)	AAL92486.1	
	VP1 protein (Sabin 3 strain)	AAL89592.1	
Streptococcus pneumoniae(PCV10)	Capsular polysaccharide biosynthesis protein [serotype 19F]	AEO88919.1	33
	Capsular polysaccharide biosynthesis protein [serotype 23F]	AAC69522.1	
	Capsular polysaccharide biosynthesis protein [serotype 18C]	CAI33577.1	
	Capsular polysaccharide biosynthesis protein [serotype 14]	CAI33319.1	
	Capsular polysaccharide biosynthesis protein [serotype 9V]	CAI33023.1	
	Capsular polysaccharide biosynthesis protein [serotype 7F]	CAI32924.1	
	Capsular polysaccharide biosynthesis protein [serotype 6B]	AAK20683.1	
	Capsular polysaccharide biosynthesis protein [serotype 5]	CAI32793.1	
	Capsular polysaccharide biosynthesis protein [serotype 1]	COS99248.1	
	Capsular polysaccharide biosynthesis protein [serotype 4]	AAK20668.1	

Amino acid sequence alignment and hot spot analysis

Identification of similar segment, including identical amino-acids and/or similar amino-acids (with similar biochemical properties), was assessed using Blastp homology search by querying the protein sequences of SARS-CoV-2 over the set of antigenic sequences of the vaccines [20]. Pairwise alignments obtained from Blastp were explored and analysed using BioEdit software, version 7.2.5 (http://www.mybiosoftware.com/bioedit-7-0-9-biological-sequence-alignment-editor.html).

Structural analysis and antigenicity prediction

The structure of the SARS-CoV-2 spike protein was obtained from the PDB entry 7BYR corresponding to 99.5% of sequence identity with QJT73034.1 entry [21]. The segments matching one of the sequences of S and N proteins were mapped on the structure. The Solvent Accessible Surface Area per residue was calculated using freesasa [21]. The T-cell epitope prediction was conducted using EpiJen [22], and the IEDB analysis resource NetMHCpan [23] methods by uploading the primary structure of SARS-CoV-2 protein. For the latter method, we have considered all the possible human HLA alleles for MHC class I. A pattern is retained if it shows a good quality local alignment with no indels and no more than two successive dissimilar residues. The matching pattern of the query has to show significant antigenicity prediction at least for one of the methods, EpiJen or IEDB NetMHCpan. For the latter we have fixed a cutoff of peptide score no less than 0.1. For EpiJen the rank of the evaluated peptide has to be located in top 10 predictions returned by the server.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable. This study did not include patients.

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files. Accession numbers of sequences used in this study are indicated in table2, in the material section of

the article. All data generated in this study are available in a public repository https://figshare.com/articles/dataset/Comparative_study_of_SARS-CoV-2_proteins_and_antigenic_proteins_in_BCG_OPV_MMR_and_other_vaccines_evidence_of_possible_putative_protective_effect/13220762

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Authors' contributions:

SH-B and KG designed the study, SH-B and HO wrote the papers, HO, RT, KA and M L contributed to carry out analysis, SH-B, IBM, MK and HT validated the study. All authors read and approved the final manuscript.

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References

1. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nature reviews Drug discovery. 2020; doi: 10.1038/d41573-020-00016-0.
2. WHO. WHO Coronavirus Disease (COVID-19) Dashboard 2020 [21 October 2020]. Available from: https://covid19.who.int/.
3. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nature microbiology. 2020; doi: 10.1038/s41564-020-0695-z.
4. Touati R, Haddad-Boubaker S, Ferchichi I, Messaoudi I, Ouesleti AE, Triki H, et al. Comparative genomic signature representations of the emerging COVID-19 coronavirus and other coronaviruses: High identity and possible recombination between Bat and Pangolin coronaviruses, Genomics. 2020; doi: 10.1016/j.ygeno.2020.07.003
5. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China, Nature. 2020; doi: 10.1038/s41586-020-2008-3.
6. WHO. Coronavirus disease (COVID-19) Weekly Epidemiological Update 2020 [22 October 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
7. Curtis N, Sparrow A, Ghebreyesus TA, Netea MG. Considering BCG vaccination to reduce the impact of COVID-19, Lancet. 2020; doi: 10.1016/S0140-6736(20)31025-4.
8. Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults, Jama. 2020; doi: 10.1001/jama.2020.8189.
9. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19), Proceedings of the National Academy of Sciences of the United States of America. 2020; doi: 10.1073/pnas.2008410117
10. Sidiq KR, Sabir DK, Ali SM, Kodzius R. Does Early Childhood Vaccination Protect Against COVID-19? Frontiers in molecular biosciences. 2020; doi: 10.3389/fmolb.2020.00120.
11. He Y, Li J, Heck S, Lustigman S, Jiang S. Antigenic and immunogenic characterization of recombinant baculovirus-expressed severe acute respiratory syndrome coronavirus spike protein: implication for vaccine design, Journal of virology. 2006; doi: 10.1128/JVI.00083-06.
12. Zhang BZ, Hu YF, Chen LL, Yau T, Tong YG, Hu JC, et al. Mining of epitopes on spike protein of SARS-CoV-2 from COVID-19 patients, Cell research. 2020; doi: 10.1038/s41422-020-0366-x.
13. Hashiguchi T, Kajikawa M, Maita N, Takeda M, Kuroki K, Sasaki K, et al. Crystal structure of measles virus hemagglutinin provides insight into effective vaccines, Proceedings of the National Academy of Sciences of the United States of America. 2007; doi: 10.1073/pnas.0707830104.
14. Tajiri K, Ozawa T, Jin A, Tokimitsu Y, Minemura M, Kishi H, et al. Analysis of the epitope and neutralizing capacity of human monoclonal antibodies induced by hepatitis B vaccine, Antiviral research. 2010; doi: 10.1016/j.antiviral.2010.04.006.
15. He Y, Zhou Y, Wu H, Luo B, Chen J, Li W, et al. Identification of immunodominant sites on the spike protein of severe acute respiratory syndrome (SARS) coronavirus: implication for developing SARS diagnostics and vaccines, Journal of immunology. 2004; doi: 10.4049/jimmunol.173.6.4050.
16. Schaecher SR, Mackenzie JM, Pekosz A. The ORF7b protein of severe acute respiratory syndrome coronavirus (SARS-CoV) is expressed in virus-infected cells and incorporated into SARS-CoV particles, Journal of virology. 2007; doi: 10.1128/JVI.01691-06.
17. Uthayakumar D, Paris S, Chapat L, Freyburger L, Poulet H, De Luca K. Non-specific Effects of Vaccines Illustrated Through the BCG Example: From Observations to Demonstrations, Frontiers in immunology. 2018; doi: 10.3389/fimmu.2018.02869.
18. Netea MG, Dominguez-Andres J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease, Nature reviews Immunology. 2020; doi: 10.1038/s41577-020-0285-6.
19. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nature reviews Immunology. 2020; doi: 10.1038/s41577-020-0337-y.
20. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool, Journal of molecular biology. 215(3) 1990 403-10. PMID: 2231712
21. Cao Y, Su B, Guo X, Sun W, Deng Y, Bao L, et al. Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells, Cell. 2020; doi: 10.1016/j.cell.2020.05.025.
22. Doytchinova IA, Guan P, Flower DR. EpiJen: a server for multistep T cell epitope prediction, BMC bioinformatics. 2006; doi: 10.1186/1471-2105-7-131.

23. Reynisson B, Alvarez B, Paul S, Peters B, Nielsen M. NetMHCpan-4.1 and NetMHCIIpan-4.0: improved predictions of MHC antigen presentation by concurrent motif deconvolution and integration of MS MHC eluted ligand data, Nucleic acids research. 2020; doi: 10.1093/nar/gkaa379.
24. Dhillon S. DTPa-HBV-IPV/Hib Vaccine (Infanrix hexa): A Review of its Use as Primary and Booster Vaccination, Drugs. 2010; doi: 10.2165/11204830-000000000-00000.
25. Heijtink RA, Bergen P, Melber K, Janowicz ZA, Osterhaus AD. Hepatitis B surface antigen (HBsAg) derived from yeast cells (Hansenula polymorpha) used to establish an influence of antigenic subtype (adw2, adr, ayw3) in measuring the immune response after vaccination, Vaccine. 2002; doi: 10.1016/s0264-410x(02)00145-7
26. Tillieux SL, Halsey WS, Sathe GM, Vassilev V. Comparative analysis of the complete nucleotide sequences of measles, mumps, and rubella strain genomes contained in Priorix-Tetra and ProQuad live attenuated combined vaccines, Vaccine. 2009; doi: 10.1016/j.vaccine.2009.01.112
27. Haro I, Perez S, Garcia M, Chan WC, Ercilla G. Liposome entrapment and immunogenic studies of a synthetic lipophilic multiple antigenic peptide bearing VP1 and VP3 domains of the hepatitis A virus: a robust method for vaccine design, FEBS letters. 2003; doi: 10.1016/s0014-5793(03)00249-7.
28. Ping LH, Jansen RW, Stapleton JT, Cohen JI, Lemon SM. Identification of an immunodominant antigenic site involving the capsid protein VP3 of hepatitis A virus, Proceedings of the National Academy of Sciences of the United States of America. 1988; doi: 10.1073/pnas.85.21.8281.
29. Harboe M, Nagai S, Patarroyo ME, Torres ML, Ramirez C, Cruz N. Properties of proteins MPB64, MPB70, and MPB80 of Mycobacterium bovis BCG, Infection and immunity. 1986; doi: 10.1128/IAI.52.1.293-302.1986
30. Seki M, Honda I, Fujita I, Yano I, Yamamoto S, Koyama A. Whole genome sequence analysis of Mycobacterium bovis bacillus Calmette-Guerin (BCG) Tokyo 172: a comparative study of BCG vaccine substrains, Vaccine. 2009; doi: 10.1016/j.vaccine.2009.01.034.
31. Wiker HG, Nagai S, Hewinson RG, Russell WP, Harboe M. Heterogenous expression of the related MPB70 and MPB83 proteins distinguish various substrains of Mycobacterium bovis BCG and Mycobacterium tuberculosis H37Rv, Scandinavian journal of immunology. 1996; doi: 10.1046/j.1365-3083.1996.d01-61.x.
32. Samuel L, Katz MD. From culture to vaccine Salk and Sabin, New England Medecine. 2004; doi: 10.1056/NEJMp048217.
33. Croxtall JD, Keating GM. Pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix; PHiD-CV), Paediatric drugs 2009; doi: 10.2165/11202760-000000000-00000.

Figures

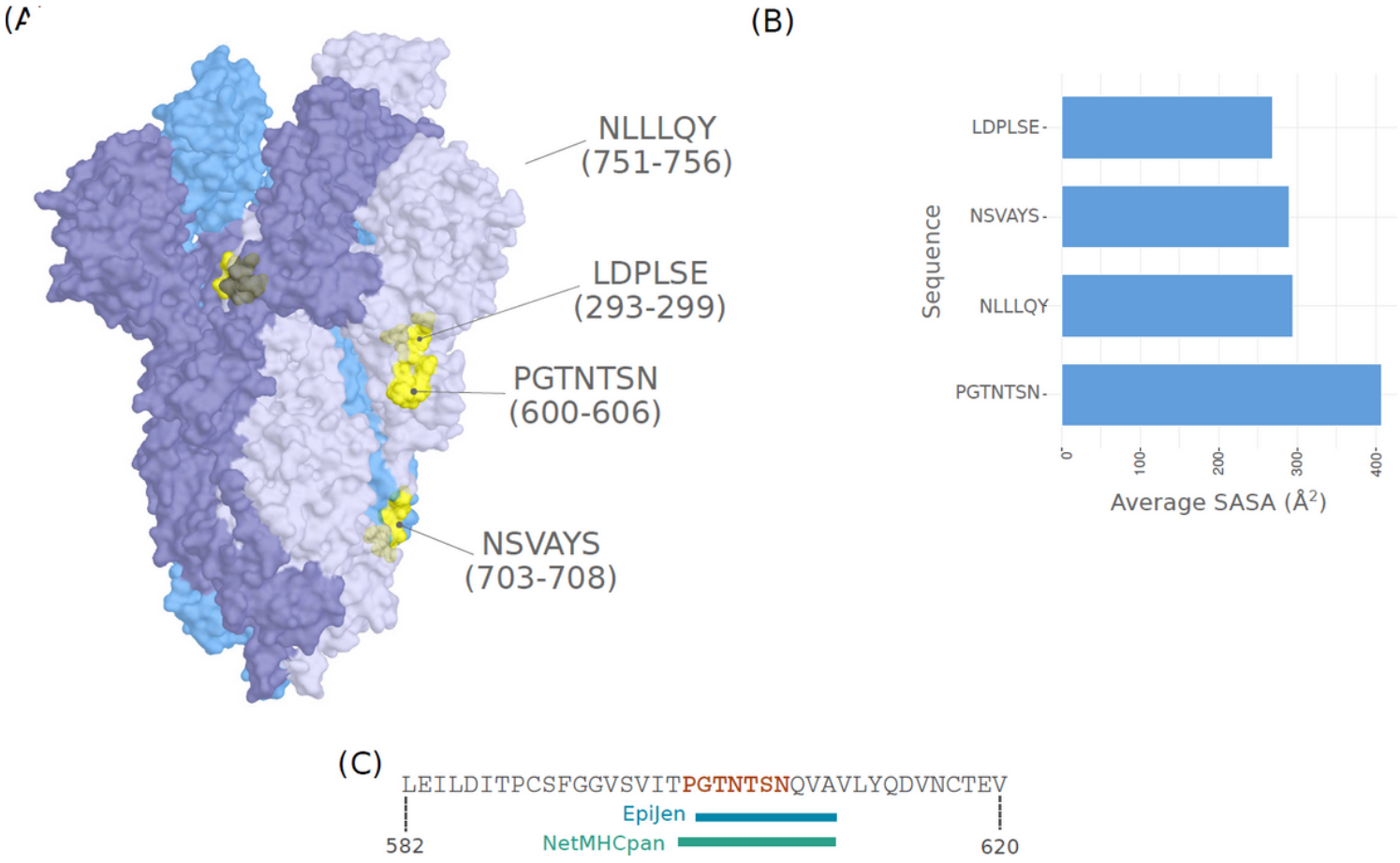

Figure 1

Structural mapping in S protein of the segments that match the antigenic proteins from different pathogens. (A) Location of the segments on the structure is marked by yellow patches. Different chains are represented in different colors. (B) Average SASA measures for each of the putative antigenic sites. (C) Location of the predicted T-cell antigenic segments by EpiJen, SYFPEITHI and MHCPred in the vicinity of PGTNTSN segment of the spike protein.

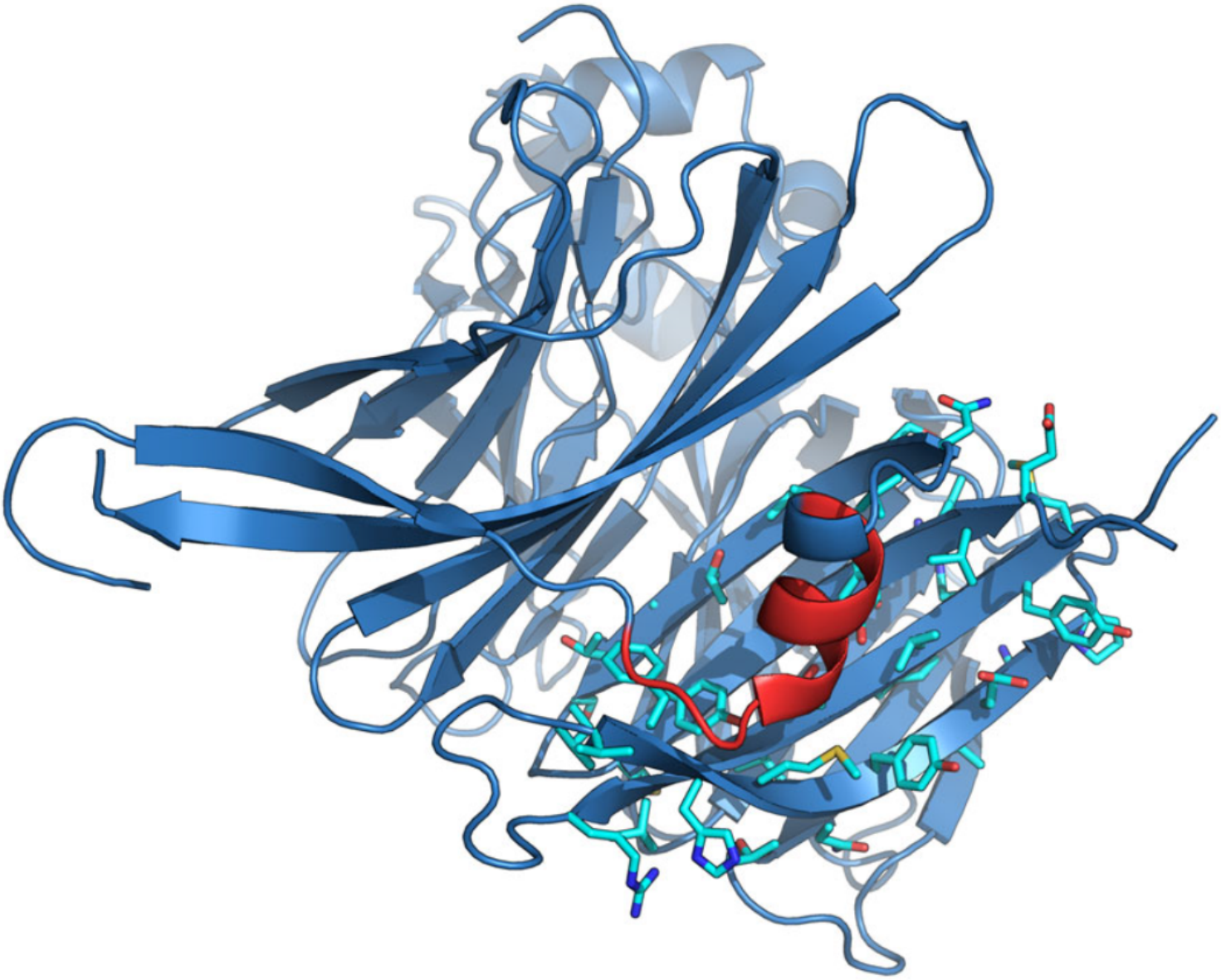

Figure 2

Crystal structure of the measles virus hemagglutinin (10.1073/pnas.0707830104). The peptide (in red) shows putative T-cell immunogenicity with the interaction pocket residues (cyan).

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