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Lessons Learned from Cutting-Edge Immunoinformatics on Next-Generation COVID-19 Vaccine Research

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Abstract

Presently, immunoinformatics and bioinformatics approaches are contributing actively to COVID-19 vaccine research. The first immunoinformatics-based vaccine construct against SARS-CoV-2 was published in February 2020. Following this, immunoinformatics and bioinformatics approaches have created a new direction in COVID-19 vaccine research. Several researchers have designed the next-generation COVID-19 vaccines using these approaches. Presently, immunoinformatics has accelerated immunology research immensely in the area of COVID-19. Hence, we have tried to depict the current scenario of immunoinformatics and bioinformatics in COVID-19 vaccine research.

Keywords Immunoinformatics · Bioinformatics · COVID-19 vaccine research · Vaccinogenomics

The COVID-19 vaccines have rolled out worldwide, and the vaccination program has started in different countries. More than 13 approved vaccine candidates are being used throughout the world for the mass vaccination program. Among them, Pfizer (BioNTech mRNA vaccine: BNT162b2) and ModernaTX mRNA vaccine (mRNA-1273) are the first approved vaccines, which have shown excellent efficacy (95% and 94.1%, respectively) (Chakraborty et al. 2021a, b). These vaccines are capable of reducing COVID-19 infection. However, DNA-based (Ad5-nCoV) and peptide-based (EpiVacCorona) vaccines are also being used for vaccination (Table S1). Most of the vaccines are based on viral S (Spike) protein as the vital vaccine antigen. If we look back at the COVID-19 vaccine research scenario, the first vaccine research against SARS-CoV-2 was initiated using immunoinformatics.

The first vaccine construct of the SARS-CoV-2 was reported in the Journal of Medical Virology on 28 February 2020 online (Bhattacharya et al. 2020a). Chakraborty and his colleagues are the first group of researchers who have developed a next-generation epitope-based peptide vaccine construct, and the vaccine construct was generated through immunoinformatics. Moreover, Chakraborty and his colleagues analyzed this vaccine's stability, safety, and efficacy through immunoinformatics, showing that this next-generation vaccine candidate is safe and immunogenic (Bhattacharya et al. 2020b). Likewise, some vaccine development companies have used immunoinformatic techniques to search for the most antigenic epitope for the vaccine candidate development.

After the beginning of COVID-19 in December 2019 in China, WHO declared a health emergency on 30 January 2020. Since then, researchers have intensified the search for therapeutics against SARS-CoV-2 (Baden and Rubin 2020). Several clinical trials have been performed in this direction, where more than 100 countries have participated. A report shows that 3754 clinical trials had been completed for COVID-19. It has been noted that some of these clinical trial results had not been updated in trial repositories (Rodgers et al. 2021). Quite a few therapeutics have given better results in clinical trials for severe COVID-19 patients

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until today. Some therapeutic molecules have proven helpful for the treatment of COVID-19, which includes remdesivir (an antiviral molecule), baricitinib (an immunosuppressive molecule), dexamethasone (an immunosuppressive molecule), and some monoclonal antibodies (Collins 2021). At first, most researchers tried to search for therapeutics by repurposing existing drugs. However, selected drugs have not provided accurate and successful outcomes. Therefore, the only way to stop the pandemic is to vaccinate the people to develop immunity against COVID-19 by using approved vaccines. Presently new SARS-CoV-2 variant (VOC; variants of concern and VOI: variants of interest) are a concern for the whole world. The vaccine candidate using alternative multi-epitopes for Wuhan strain and significant variant can be a solution (Bhattacharya et al. 2021). Collectively, it has been well accepted that the vaccine is the only effective option to stop this pandemic situation.

Immunoinformatics and bioinformatics have a significant role in COVID-19 vaccine research, especially in antigenic epitopes selection and vaccine construct development (Fig. 1). Bioinformatics, immunoinformatics, vaccinogenomics, structural biology, and molecular dynamics simulations have contributed significantly to COVID-19 vaccine research. It was observed that several vaccine constructs were developed using immunoinformatics and bioinformatics. We performed PubMed search and found that approximately 24 vaccine constructs have been developed through immunoinformatics and bioinformatics to date (Table 1). Simultaneously, several scientists identified T cell epitopes, B cell epitopes, and common T and B cell epitopes (Table 2) (Chakraborty et al. 2021c). The selected epitopes have suggested that the identified common epitopes can be used for vaccine construct development. However, the researchers did not further analyze the identified epitopes to develop vaccine constructs, having several essential parameters like allergenicity and immunogenicity, utilizing immunoinformatics and bioinformatics.

It was observed that only a few groups of scientists developed the vaccine construct against SARS-CoV-2 and performed docking with the Toll-like Receptor (TLR) group of molecules to understand the TLR based downstream regulation of the protective/adaptive immunity. Simultaneously, quite a few scientists have analyzed the complex stability with molecular dynamics simulation. Furthermore, we have found that a small number of scientist groups evaluated the vaccine construct's allergenicity

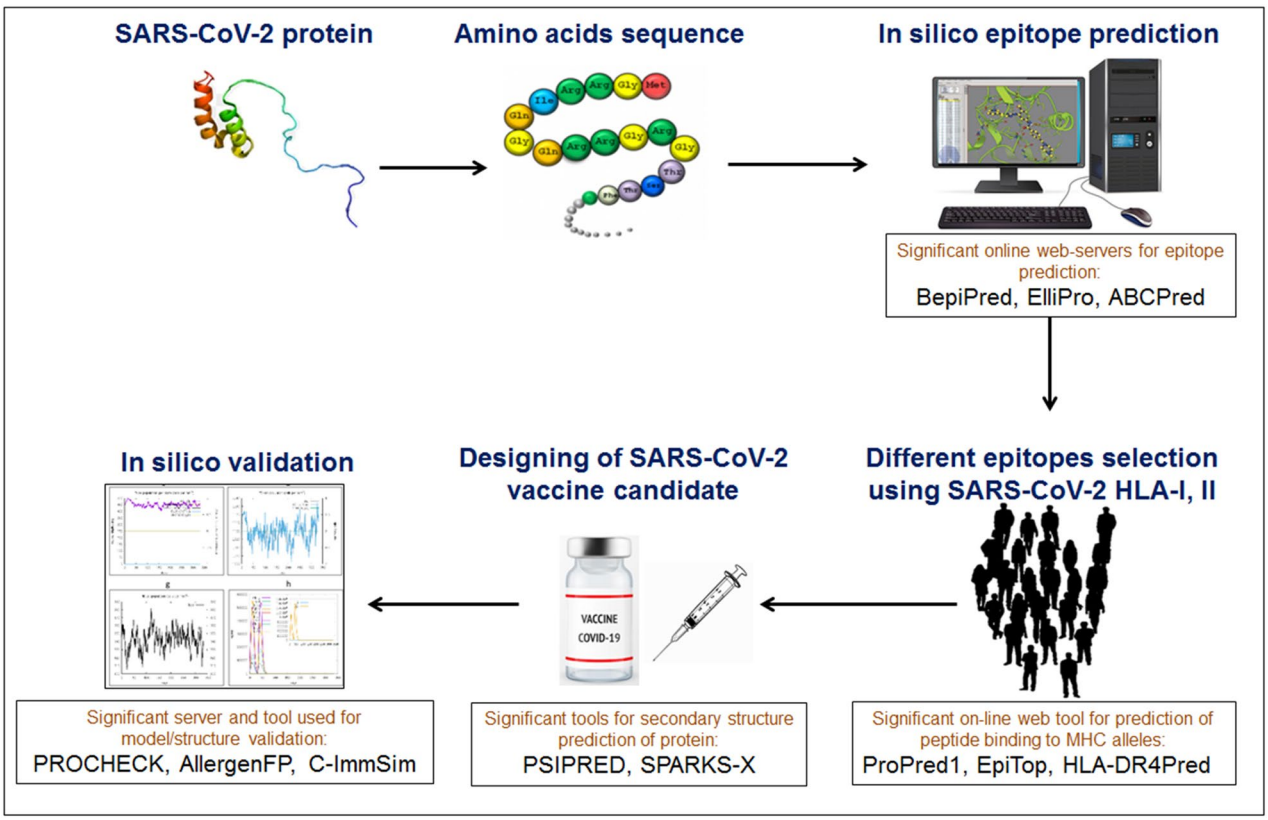

Fig. 1 Schematic representation showing a flowchart of next-generation COVID-19 vaccine development through immunoinformatics. We have highlighted different tools, databases and servers which are using by the researchers for the vaccine development through immunoinformatics

Table 1 Different immunoinformatics and bioinformatics research on next generation vaccine construct development against SARS-CoV-2

Sl. no.	Researcher	Country	Nos. epitopes	Contributing viral proteins	Remarks	References
1.	Bhattacharya M., et al., 2020	India, South Korea	19 epitopes	Spike glycoprotein	Peptide-based multi-epitopic vaccine contrast from S-protein	Bhattacharya et al. (2020a)
2.	Kalita P., et al., 2020	India, Japan	33 epitopes	Nucleocapsid protein, membrane glycoprotein, surface spike glycoprotein	Multi-epitopic peptide-based subunit vaccine designed	Kalita et al. (2020)
3.	Qamar M., et al., 2020	China, Pakistan	27 epitopes	Envelope protein, membrane glycoprotein, nucleocapsid protein	Designed a 505 amino acids containing effective multi-epitope vaccine	ul Qamar et al. (2020)
4.	Saha R., et al., 2021	India	16 epitopes	Spike glycoprotein	B cell-derived T cell epitopes peptide based vaccine construct	Saha et al. (2021)
5.	Yazdani Z., et al., 2020	Iran	6 epitopes	Spike glycoprotein, membrane glycoprotein, nucleocapsid phosphoprotein, envelope protein	Vaccine construct consists of immunodominant multi-epitopes from viral structural proteins	Yazdani et al. (2020)
6.	Jain N., et al., 2020	India	29 epitopes	Nucleocapsid protein, surface glycoprotein, membrane protein, envelope protein	Multi-epitope peptide based vaccine candidate against SARS-CoV-2	Jain et al. (2021)
7.	Dong R., et al., 2020	China	44 epitopes	Nucleocapsid phosphoprotein, envelope protein, endoRNAse membrane glycoprotein	Multi-epitopic vaccine developed from T and B cell epitopes of S-protein	Dong et al. (2020)
8.	Kumar A., et al., 2020	India	56 epitopes	Nucleocapsid protein, Envelope protein, spike glycoprotein	Prediction and selection of multi-epitope, and in silico cloning of vaccine construct	Kumar et al. (2020)
9.	Khairkhah N., et al., 2020	Iran	46 epitopes	Spike glycoprotein, nucleocapsid protein, membrane protein	Three multi-epitope constructs for peptide based vaccine candidate	Khairkhah et al. (2020)
10.	Samad A., et al., 2020	Bangladesh, Saudi Arabia	6 epitopes	Spike glycoprotein	Multi-epitopic subunit vaccine construction and structural evaluation	Samad et al. (2020)
11.	Qamar M., et al., 2020	China, Pakistan	13 epitopes	Surface glycoprotein, envelope protein, and membrane glycoprotein	Multi-epitopic peptide vaccine construction and in silico cloning	Tahir ul Qamar et al. (2020)
12.	Fatoba A., et al., 2021	South Africa, Nigeria	18 epitopes	Surface and membrane glycoproteins	Design of multi-epitope vaccine from surface and membrane glycoprotein	Fatoba et al. (2021)
13.	Mahapatra S.R., et al., 2020	India	20 epitopes	Spike protein, envelope protein, membrane protein, nucleocapsid protein	Epitope selection from multiple glycoproteins and vaccine construction	Mahapatra et al. (2020)
14.	Behmard E., et al., 2020	Iran	46 epitopes	Spike glycoprotein, envelope protein, membrane protein, and nucleocapsid phosphoprotein	Construction and molecular modeling of multi-epitopic peptide vaccine	Behmard et al. (2020)
15.	Oladipo E.K., et al., 2021	Nigeria	15 epitopes	Surface glycoprotein	Conserved peptide-based antigenic, non-toxic and non-allergic subunit vaccine	Oladipo et al. (2021)

Table 1 (continued)

Sl. no.	Researcher	Country	Nos. epitopes	Contributing viral proteins	Remarks	References
16.	Srivastava S., et al., 2020	India	103 epitopes	ORF proteins	Multi-patch protein vaccine constructs	Srivastava et al. (2020)
17.	Albagi S., et al., 2020	Sudan, India, Turkey	6 epitopes	Nucleocapsid phosphoprotein and spike glycoprotein	Peptides vaccine designed from the nucleocapsid phosphoprotein and S- protein	Abd Albagi et al. (2020)
18.	Ghorbani A., et al., 2020	Iran	10 epitopes	Spike glycoprotein	Virus-like particle based vaccine developed from epitopes of S-protein	Ghorbani et al. (2020)
19.	Waqas M., et al., 2020	Pakistan	28 epitopes	Main protease	Multi-epitopic peptide vaccine construct from SARS-CoV-2	Waqas et al. (2021)
20.	Abduljaleel Z., et al., 2020	Saudi Arabia, Canada	12 Epitopes	Spike protein, membrane glycoprotein, envelop protein and nucleocapsid protein	Vaccine construct developed by antigenic epitope peptides fragments	Abduljaleel et al. (2021)
21.	Khan T., et al., 2021	Bangladesh, USA	26 epitopes	Nucleocapsid protein, membrane protein, envelope protein, spike, protein, ORF and non-structural proteins	Effective peptide-based multi-epitope vaccine	Khan et al. (2021b)
22.	Lim H., et al., 2020	Malaysia	7 epitopes	Spike glycoprotein, nucleocapsid protein, membrane protein	Vaccine construct from conserved peptides epitopes	Lim et al. (2020)
23.	Rahman N., et al., 2020	Pakistan, Czech Republic	4 epitopes	Surface glycoprotein	Peptide-based multi-epitope five vaccine constructs developed	Rahman et al. (2020)
24.	Sanami S., et al., 2020	Iran	18 epitopes	Spike protein	Vaccine development from the T and B cell epitopes of S-protein	Sanami et al. (2020)
25.	Bhattacharya M., et al., 2021	India, South Korea	23 epitopes	Spike protein	Multi-epitopic peptide vaccine construct against the Wuhan variant and all significant mutant variants of SARS-CoV-2	Bhattacharya et al. (2021)
26.	Khan et al., 2021	China, Pakistan, Kuwait	11 epitopes	Spike protein	Multi-epitopes subunit vaccine from the S- protein of the SARS-CoV-2 new variants	Khan et al. (2021a)

Table 2 Different immunoinformatics and bioinformatics approaches on epitopes identification towards SARS-CoV-2 vaccine research

Sl. no.	Researcher	Country	Nos. epitopes	Contributing viral proteins	Remarks	References
1.	Joshi A., et al., 2020	India	9 epitopes	Envelope protein, nulceocapsid phosphoprotein, membrane glycoprotein ORF-3a and ORF-7a	Putative epitope selection from SARS-CoV-2 against HLA allelic proteins	Joshi et al. (2020)
2.	Singh J., et al., 2021	India	5 epitopes	Spike glycoprotein	Potential linear, structural B cell epitope and T cell epitopes were predicted from eight different SARS-COV-2 strain	Singh et al. (2021)
3.	Kiyotani K., et al., 2020	Japan	3412 epitopes	Spike, envelope, membrane, and nucleocapsid proteins, nonstructural proteins (6 ORF)	Identified numbers of possible peptide epitopes from SARS-COV-2 structural and nonstructural proteins	Kiyotani et al. (2020)
4.	Oliveira S C., et al., 2020	Brazil, United States	135 epitopes	Nucleocapsid Protein	Major B and T cell epitopes are predicted from the SARS-CoV-2 nucleocapsid protein	Oliveira et al. (2020)
5.	Chen H., et al., 2020	China	63 epitopes	Spike protein, nucleocapsid protein	B cell epitopes and T cell epitopes were predicted from SARS-CoV-2 S-protein and N protein	Chen et al. (2020)
6.	Wang D., et al., 2020	China, USA	71 epitopes	Spike protein	Potential B cell and T cell epitopes from S- protein were predicted for vaccine design	Wang et al. (2020)
7.	Lin L., et al., 2020	China	30 epitopes	Surface glycoprotein, membrane glycoprotein and nucleocapsid protein	T cell epitopes and B cell epitopes identified from multiple protein segment of SARS-CoV-2	Lin et al. (2020)
8.	Rakib A., et al., 2020	Bangladesh, Indonesia, Morocco, Saudi Arabia	10 epitopes	Spike glycoprotein	Optimal epitopes were identified from S- protein of SARS-CoV-2	Rakib et al. (2020)
9.	Jakhar R., et al., 2020	India	10 epitopes	Envelope protein	Epitopes were identified from envelope protein of SARS-CoV-2	Jakhar and Gakhar (2020)
10.	Lizbeth R., et al., 2020	México	4 epitopes	Spike glycoprotein	Identified four epitopes from SARS-CoV-2 S-protein	Lizbeth et al. (2020)
11.	Mukherjee S., et al., 2020	Israel	17 epitopes	Membrane glycoprotein, nucleocapsid phosphoprotein, spike glycoprotein	Epitopes were identified from whole genome and proteome of SARS-CoV-2	Mukherjee et al. (2020)
12.	Crooke S., et al., 2020	USA	47 epitopes	Spike glycoprotein, envelope protein, membrane protein	Identified T cell epitopes and B cell epitopes from structural, non-structural and accessory proteins of SARS-CoV-2	Crooke et al. (2020)
13.	Ranga V., et al., 2020	Finland	15 epitopes	RNA-dependent RNA polymerase, membrane glycoprotein, envelope protein, nucleocapsid phosphoprotein, 3C-like proteinase, surface glycoprotein, ORF and other non-structural protein	Epitopes were identified from 26 protein sequences encoded by the SARS-CoV-2 genomic sequence	Ranga et al. (2020)
14.	Ashik A., et al., 2020	Bangladesh	3 epitopes	Spike glycoprotein	Altered epitopes were predicted from the S-protein of SARS-CoV-2	Ashik et al. (2020)

Table 2 (continued)

Sl. no.	Researcher	Country	Nos. epitopes	Contributing viral proteins	Remarks	References
15.	Baruah V., et al., 2020	India	13 epitopes	Surface glycoprotein	Multiple, conserved epitopes were identified in the SARS-CoV-2	Baruah and Bose (2020)
16.	Bhattacharya M., et al., 2020	India, South Korea	4 epitopes	Spike glycoprotein	Common (B and T cell) epitopes were identified from the S-protein of SARS-CoV-2	Bhattacharya et al. (2020c)
17.	Tilocca B., et al., 2020	Italy	8 epitopes	Envelope protein	Epitopes having high antigenicity were mapped and characterized from SARS-CoV-2	Tilocca et al. (2020)
18.	Rencilin CF., et al., 2020	India, USA	18 epitopes	ORF, envelope protein, membrane glycoprotein, nucleocapsid Phosphoprotein	Conserved epitopes were identified from the complete proteome of SARS-CoV-2	Rencilin et al. (2021)
19.	Lon JR., et al., 2020	China	7 epitopes	spike protein, envelope protein and membrane protein	Seven epitopes were predicted from the nucleocapsid phosphoprotein of SARS-CoV-2	Lon et al. (2020)
20.	Ong E., et al., 2021	USA	301 epitopes	Spike protein	Numbers of T cell epitopes were identified from S-protein of SARS-CoV-2	Ong et al. (2021)

and immunogenicity. Even few researchers have performed normal mode analysis (NMA) analyses, in-silico cloning of vaccine candidates, and analyzed the physicochemical properties using immunoinformatics and bioinformatics. Analysis of the physicochemical properties is necessary to understand the solubility, molecular weight, theoretical isoelectric point (pI), estimated half-life, instability index, aliphatic index, and grand average of hydropathicity (GRAVY) of the vaccine candidate. All these steps are very crucial for evaluating a successful vaccine construct while utilizing bioinformatics and immunoinformatics.

On 10 January 2020, the Chinese research group was the first to sequence the SARS-CoV-2 genome. Zhang and his colleagues sequenced the genome at Fudan University and made it publicly available in GenBank (Fan et al. 2020; Triggle et al. 2020). After the availability of the genome sequence in GenBank, several researchers started to identify the antigenic epitopes using the sequence through immunoinformatics and bioinformatics. Immunoinformatics approaches for COVID-19 vaccine research were triggered because of two reasons. Firstly, this approach can design the vaccine rapidly (Fig. 2). Secondly, there was an urgency for the COVID-19 vaccine throughout the globe. Most researchers targeted viral spike (S)-protein in their vaccine design analysis to identify the epitopes as it was found from the previous studies that S-protein has the maximum antigenic epitope regions (Dai and Gao 2020). In addition, the previous studies have also shown that S glycoprotein in the other coronaviruses (SARS-CoV-1, MERS-CoV-2) has the highest antigenic epitopes. So, this knowledge of the prior research helped the researchers to develop the COVID-19 vaccine candidates quickly. Alternatively, several researchers also tried to identify epitopic areas from other structural proteins (M protein, E protein, N protein)/ proteome along with S-protein.

We have performed a comprehensive, advanced search on PubMed with the keywords "immunoinformatics" and "COVID-19" and found that 88 articles have been published so far on this topic (Fig. 3). Most of the article deals with the immunoinformatics-based vaccine development, the safety and efficacy analysis of vaccine construct, and different immunological component analyses related to SARS-CoV-2. The immunoinformatics approach has also been applied to find out different vaccine constructs for other coronaviruses (SARS-CoV-1, MERS-CoV-2). Few of them even have tried to develop a trivalent subunit vaccine construct for three emerging coronaviruses using immunoinformatics approaches. Several immunoinformatic databases have been developed to illustrate the immunogenicity and virulence of glycoproteins of coronaviruses and others. One such example of a database is DBCOVP which provides the information about

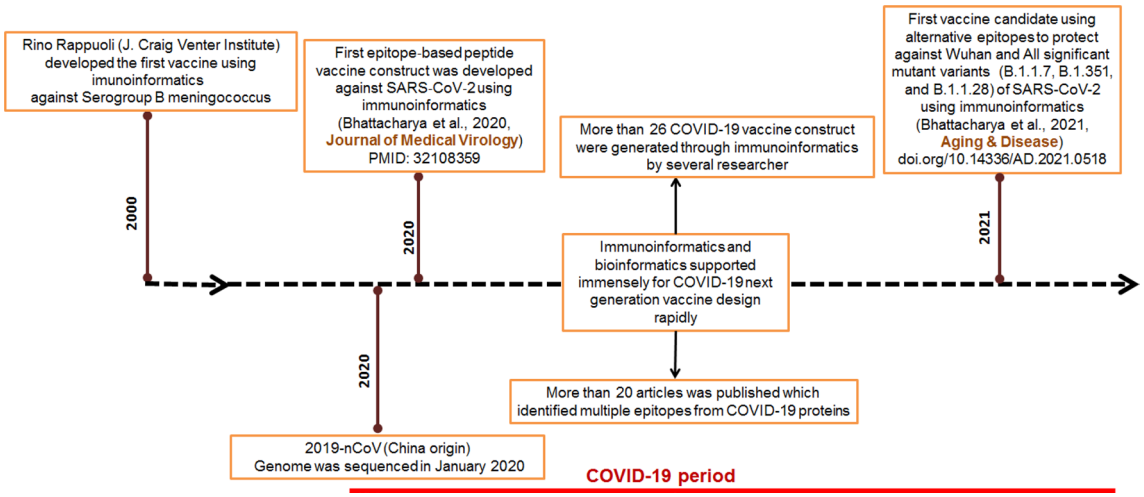

Fig. 2 Some important milestone of immunoinformatics and bioinformatics studies that stimulated the next-generation vaccine research against SARS-CoV-2

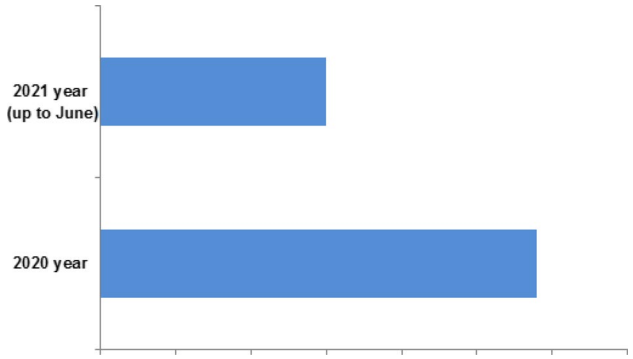

Fig. 3 PubMed search using keywords "immunoinformatics" and "COVID-19" which illustrated the number of publications of immunoinformatics based COVID-19 research in the year of 2020 and 2021 (up to June)

conserved B cell, and T cell epitopes predicted from the protein (Sahoo et al. 2021).

Epitope-based COVID-19 vaccines are the next-generation COVID-19 vaccines, posing a highly antigenic part and an adjuvant. The antigenic component is also selected through the common epitopes (B and T cell) selection procedure. It can be more effective in generating adaptive immunity. Also, the vaccine can trigger innate immunity and stimulate the secretion of protective cytokines through interaction with TLRs. However, these vaccines have shown some limitations. One such limitation observed was blood clot formation after using the COVID-19 vaccine made by AstraZeneca (Wolf et al. 2021). Other types of vaccines (live attenuated COVID-19 vaccine) also have some limitations. For example, live attenuated vaccines may suffer secondary mutation, which can revive virulence from the attenuated microorganism and lead to the occurrence of disease.

Immunoinformatics is now at the forefront of the development of the next-generation COVID-19 vaccine. Recently, Ishack and Lipner have published a significant commentary that described the immense role of immunoinformatics and bioinformatics on COVID-19 vaccine development (Ishack and Lipner 2021). However, there are several challenges ahead for immunoinformatics in vaccine research that need to address instantly. Firstly, advancement in the development of algorithms for immunoinformatics and bioinformatics. These algorithms will help to perform a more accurate and faster calculation without any computational errors. Secondly, some algorithms are available to illustrate the adaptive and innate immunity scenario after vaccination; however, more research data (in vitro and in vivo) is required to validate their claim. Thirdly, consideration of several factors associated with effective multi-epitope vaccine construct activity, such as the combination of epitopes and peptide linkers. One such example is that the stability of the vaccine candidate depends on the linker peptide. Fourthly, no epitope-based vaccine has thrived against some diseases until today (e.g., HIV, malaria). For these diseases, the causative organism possesses several antigenic proteins. In these cases, epitopes of these proteins are not adequately mapped, and the highly potent antigenic protein is difficult to identify. Therefore more extensive researches are required in this direction. However, soon, immunoinformatics will address all the challenges for COVID-19 vaccine research and help to design next-generation vaccines for all the infectious diseases and neglected diseases in coming times.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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