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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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.
| 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 epitope 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 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, 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)         |
| 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, envelope 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) |
| Sl. no. | Researcher                  | Country                        | Nos. epitopes | Contributing viral proteins                                                                 | Remarks                                                                                     | References          |
|--------|----------------------------|--------------------------------|---------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------|
| 1.     | Joshi A., et al., 2020     | India                          | 9 epitopes    | Envelope protein, nucleocapsid 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 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                        | B 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) |
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
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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