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Immunoinformatics Approach for the Identification and Characterization of T Cell and B Cell Epitopes towards the Peptide-Based Vaccine against SARS-CoV-2

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Presently, immunoinformatics is playing a significant role in epitope identification and vaccine designing for various critical diseases. Using immunoinformatics, several scientists are trying to identify and characterize T cell and B cell epitopes as well as design peptide-based vaccine against SARS-CoV-2. In this review article, we have tried to discuss the importance in adaptive immunity and its significance for designing the SARS-CoV-2 vaccine. Moreover, we have attempted to illustrate several significant key points for utilizing immunoinformatics for vaccine designing, such as the criteria for selection and identification of epitopes, T cell epitope, and B cell epitope prediction and different emerging tools/databases for immunoinformatics. In the current scenario, a few immunoinformatics studies have been performed for various infectious pathogens and related diseases. Thus, we have also summarized and included these current immunoinformatics studies in this review article. Finally, we have discussed about the probable T cell and B cell epitopes and their identification and characterization for vaccine designing against SARS-CoV-2.

Key Words: Immunoinformatics, T cell epitopes, B cell epitopes, Vaccine design, SARS-CoV-2.

Introduction

The use of modern technologies in the field of biological sciences is generating an enormous amount of data and making a significant impact on different branches of life sciences. This large amount of data is creating new opportunities for the researcher, especially in the field of bioinformatics (1). Recently, EMBL-EBI has reported that a vast amount of biological data is stored into servers, and it is doubling every year (1,2). The bioinformatics researchers are currently utilizing and analyzing large amounts of biological data to generate the various probable working model for every field of science. Therefore, simultaneously, there has been a massive growth in the field of bioinformatics, and research are analyzing the data from different domains of biological science.

Similarly, an enormous amount of experimental data is also being generated in the field of immunological research. Therefore, bioinformatics applications of analyzing the considerable amount of experimental data related to immunology research might provide new possibilities around diagnostics and vaccines. Bioinformatics can generate various kinds of software and servers for analyzing the immunological data, and at the same time, these software and servers are capable of understanding the properties of the immune system. So, the rapid growth of bioinformatics has been noted in the field of immunology, and this has led to the formation of a new branch of bioinformat-

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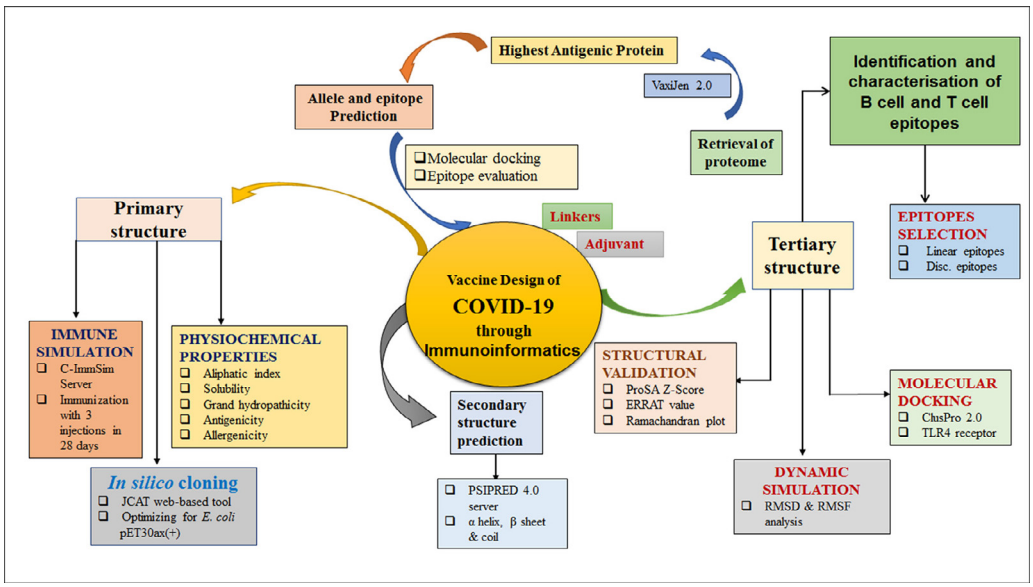

Figure 1. A schematic diagram to illustrate identification and characterization of T cell and B cell epitopes towards the peptide-based vaccine designing against SARS-CoV-2

ics called computation immunology. However, computation immunology is now termed as "Immunoinformatics" (3). These days, it is an essential element in the field of immunological research and is providing a platform for processing and understanding the different immunological events.

Immunoinformatics helps in the identification of B cell and T cell epitopes. The potential of different B and T cell epitopes were identified and characterized using various immunoinformatics tools utilizing viruses and bacteria from time to time. Ahmad B, et al. identified and characterized potential B and T cell epitopes from ebolavirus glycoprotein (4). Possible B and T cell epitopes from Leishmania secretory proteins were identified and characterized by Khatoon N, et al (5). Narula A, et al. also identified and characterized potential B and T cell epitopes from chikungunya for multi-epitopic vaccine development (6). Usually, immunoinformatic identified and characterized B and T cell epitopes are used for multi-epitopic vaccine development.

The immunoinformatics helps in vaccine development, and this has been termed as reverse vaccinology (7). This process has speeded up the design of a multi-epitope vaccine development using different antigenic constructs. The discovery of many unknown antigens has shown a successful way to vaccine development though immunoinformatics. The process of reverse vaccinology using immunoinformatic tools can usually decipher different antigenic functions. Moreover, to understand the biology of the pathogen and mutagenic antigens, immunoinformatic tools are a boon in the world of vaccine development. Therefore, this next-generation methodology could address the challenges faced while handling pathogens with mutagenic antigens. It can provide a solution against these pathogens through the development of the multi-epitope vaccine utilizing either a mutagenic antigen or the normal antigen (8,9).

COVID-19 has created a health emergency throughout the globe. This disease has created a pandemic situation in several countries throughout the world, and deaths associated with its complications are increasing day by day (10–12). Scientists are rigorously trying to search for new therapeutics and vaccines against COVID-19. However, with continuing efforts, only a limited number of therapeutics have been are mapped, such as remdesivir, tocilizumab, lvermectin, and dexamethasone (11,13–15). To combat COVID-19, a vaccine is the only desired way, and every country is focused on the development of some potent vaccine against it. Sooner or later, the world will get a new vaccine against SARS-CoV-2 (16,17). Immunoinformatics has been used by several groups of research to map antigens of SARS-CoV-2 (Figure 1). Lately, many immunoinformatics studies have been performed to determine the epitopes by using already identified B and T cells epitope database.

In this article, we have discussed the adaptive immunity and its importance for SARS-CoV-2 vaccine design. Also, an emphasis has been given to the topics like the epitopes selection criteria, identification of epitopes, B cell epitope prediction, T cell epitope prediction, different emerging tools, and databases for immunoinformatics. Here, immunoinformatics related studies for different pathogenic diseases have also been illustrated. Finally, we have discussed the B cell and T cell epitopes identification and characterization for vaccine designing against SARS-CoV-2.

Adaptive Immunity and its Importance for SARS–CoV-2 Vaccine Design

The adaptive immunity or adaptive immune system is also referred to as acquired immunity. Acquired immunity has two components: i) the cellular immune response through the T lymphocytes or T cells, and ii) the humoral response of antibody produces through the B lymphocytes or B cells. An antigen is a small portion of a protein that can elicit an immune reaction and is often termed as an epitope. These epitopes can be recognized by the consequent B cell receptor (BCR) or T cell receptor (TCR) present on B or T cells. B cell epitopes are composed of contiguous amino acids and linear amino acids. Conversely, T cell epitopes are noted as small linear peptides that are cleaved from antigenic proteins (18,19). There are two major subsets of the T cell population, which can be differentiated through the presence of any of two glycoproteins on their surface, i.e., CD4 or CD8 (13).

$CD4^+$ T cells act as T helper cells (Th cell), and this group of cells can recognize the peptides exhibited by MHC class II molecules (major histocompatibility complex). T helper cells could produce cytokines (18,19). Similarly, $CD8^+$ T cells act as T cytotoxic cells (Tc cell), and this group of cells can recognize the peptides exhibited by MHC class I molecules. T cytotoxic cells have cytolytic activity and cause apoptosis of virally infected cells (18,19).

Like all viral infections, the adaptive immune response may play an important role during the infection of SARS-CoV-2. The T lymphocytes can provide an inflammatory response and produce different kinds of cytokines against SARS-CoV-2. On the other hand, B lymphocytes can produce specific antibodies against SARS-CoV-2 and can help to neutralize the virus.

We all know that the IgG (immunoglobulins G) is vital for immune memory and long-term immunity. Similarly, IgM (immunoglobulins M) can provide the first line of defense during viral infections. Thus, these two are essential components against SARS-CoV-2 and can only be generated through vaccination or adaptive immune system (20).

Epitopes Selection for Immunoinformatics Study and its Infusing Factors

Epitopes selection is one of the critical steps for immunoinformatics study. During epitope selection, we should select epitopes that are multi-specific and broad-based (21). Multi-specific epitopes may be identified from the multiple proteins originating from a single pathogen. Similarly, broad-based epitopes are a range of epitopes that are derived from a single protein. While selecting significant epitopes, different factors might affect the selection procedure and should be considered for assessing the various abilities of epitopes. The factors include the attachment capacity of an epitope with a suitable MHC molecule (an important factor for selection), the capability of an epitope for cellular presentation, and the T cell repertoire should be able to distinguish the MHC-epitope complexes (22,23).

Immunoinformatics and Identification of Epitopes

The identification of suitable epitopes is the most notable step for multi-epitope vaccine designing. *In silico* study requires to evaluate the sequences of amino acid from a pathogen and to find out the specific motif. It should have a high binding affinity, particularly to MHC molecules (24,25).

T cell Epitope Prediction Though Immunoinformatics

For immunoinformatics based T cell epitope prediction, several immunoinformatics-based algorithms were developed (26–28). Immunoinformatics based T cell epitope prediction includes two methods, which can be either direct or indirect. The direct method of T cell epitope prediction is based on any of the three types of patterns, which includes, i) epitope motif pattern, ii) amphipathic based pattern, and iii) mix epitopic pattern (23,29). There is a disadvantage of the direct method of T cell epitope prediction as it is the low accuracy.

It has been noted that indirect methods were predicted using MHC binders in comparison to T cell epitopes. However, the prediction of MHC class I binders is easy to compare than the MHC class II binders. Due to the presence of binding grooves in the MHC class II molecules, the prediction is more complicated. The indirect method of T cell epitope prediction is based on different methods such as quantitative matrices-based methods, neural networks-based methods, motif profiles-based methods, motif pattern-based methods, MHC-peptide threading-based method, support vector machines based methods, free energy scoring functions based methods and 3D-QSAR studies (23,30,31). Some web-based computational system tools for T cell epitope prediction are easy to accessible like MULTIPRED (32), TEPITOPEpan (33), Pickpocket (34).

Prediction of B cell Epitopes Through Immunoinformatics

It has been noted that BCR present on the B-cell can recognize B cell epitopes. The B cell epitopes are the antigenic regions that are present on the surface of any pathogen. This recognition of the antigen can activate B-cell for the generation of specific antibodies against the recognized antigen. Hence, it is necessary that we should consider B cell epitopes when we design successful vaccines against any pathogen. However, there are two groups of B cell epitopes, which are discontinuous epitopes and continuous or linear epitopes. It has been es-

Table 1. Different immunoinformatics and related tools/ web server/ database and their web address

Sl. no	Web server/Tool/Database description	Name	Web address	Reference
1	Prediction of linear B cell epitopes	LBtope	http://crdd.osdd.net/raghava/lbtope/	(57)
2	Prediction of antibody specific B cell epitopes	IgPred	http://crdd.osdd.net/raghava/igpred/	(58)
3	Artificial neural network-based B cell epitope prediction server	Abcpred	https://webs.iiitd.edu.in/raghava/abcpred/	(59)
4	Prediction of linear B cell epitopes, using physico-chemical properties	Bcepred	https://webs.iiitd.edu.in/raghava/bcepred/	(60)
5	Sequential B-cell Epitope Predictor	BepiPred	http://www.cbs.dtu.dk/services/BepiPred/	(61)
6	Residue-level epitope mapping of antigens based on peptide microarray data.	ArrayPitope	http://www.cbs.dtu.dk/services/ArrayPitope/	(62)
7	Prediction of discontinuous B cell epitopes from protein three dimensional structures.	DiscoTope	http://www.cbs.dtu.dk/services/DiscoTope/	(63)
8	Database of experimentally characterized immune epitopes	Immune Epitope Database (IEDB)	https://www.iedb.org/	(64)
9	Integrated knowledge resource specialized in the antibodies, T cell receptors, major histocompatibility complex	IMGT®	http://www.imgt.org/	(65)
10	Prediction of protective antigens and subunit vaccines.	VaxiJen	http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html	(39)
11	Prediction of Cytotoxic T Lymphocyte epitopes	CTLPred	http://crdd.osdd.net/raghava/ctlpred/index.html	**(66)**
12	Prediction of MHC class-II binding regions in an antigen sequence	ProPred	https://webs.iiitd.edu.in/raghava/propred/	(67)
13	Identifying the MHC class-I binding regions in antigens	ProPred-I	https://webs.iiitd.edu.in/raghava/propred1/	(68)
14	Structural database and viewing tools, MHC/peptide/TCR combinations	PDB	https://www.rcsb.org/	(69)
15	Secondary structure prediction of the vaccine	PSIPRED	http://bioinf.cs.ucl.ac.uk/psipred/	(70)
16	Allergenicity prediction of protein	AllerTOP	https://www.ddg-pharmfac.net/AllerTOP/	(71)
17	Reverse translation and codon optimization	JCat	http://www.jcat.de/	(72)
18	Analyze immunogenicity and immune response properties in mesoscopic level	C-ImmSim	http://www.cbs.dtu.dk/services/C-ImmSim-10.1	(73)
19	In silico cloning of vaccine	WebDSV	http://www.molbiotools.com/WebDSV/	(74)
20	Solubility prediction of protein	Protein-Sol	https://protein-sol.manchester.ac.uk/	(75)
21	Predict and design toxic/non-toxic peptides	ToxinPred	http://crdd.osdd.net/raghava/toxinpred/	(76)

timated that more than 85% of the B cell epitopes are continuous in sequence (35). During linear B cell epitope prediction, researchers consider some of the properties of amino acids, such as secondary structure, amino acid charge, exposed surface area, and hydrophilicity (23,31).

Some continuous B cell epitopes prediction tools or servers are available for the immunoinformatics research are BCPRed, FBCPred (36), and COBEpro (37).

Emerging Immunoinformatics Tools Used for Vaccine Designing

Several immunoinformatics tools are being used for the identification of the probable epitopes for vaccine development (Table 1). Some examples include Vaxign and VaxiJen. Vaxign helps in the vaccine target prediction as well as the analysis (38), while VaxiJen helps in the prediction of antigens (39). Some of these immunoinformatics tools can search the protein sequences and identify the MHC binding motifs for the epitopes. The identified epitopes (from B cell and T cells) are used to develop the probable epitope-based vaccine. This vaccine can be used among different human populations, even if the genetic variability among these populations has been observed (23,40).

Emerging Immunoinformatics Databases Used for Vaccine Designing

Currently, several available databases can provide an extensive range of immunological information in diverse areas of immunology. Different immunoinformatics data originated from the immunological studies are stored in the databases (Table 1). Some immunoinformatics databases are Bcipep, SYFPEITHI, and several others. Bcipep is a repertoire that consists of a data source about B cell epitopes (41). YFPEITHI is databank for MHC peptide motifs and MHC ligands (42). All these types of databases are continually helping the advancement of immunoinformatics (23,40).

Immunoinformatics Related Studies to Understand Different Infectious Diseases and its Pathogen

Immunoinformatics based studies have been performed to understand different diseases (Table 2). These studies have

Table 2. Different immunoinformatics studies to understand diverse infectious diseases and its pathogen

Sl. no	Researcher group	Country of origin	Human pathogen	Target protein	Remarks	Reference
1	Chaudhuri D, et al. 2020	India	Hepatitis B virus, and Hepatitis C virus	Viral protease, core, and membrane protein	Identified T cell, B cell epitopes and designing a common peptide-based vaccine	(77)
2	Saha CK, et al. 2017	Bangladesh	Hendra virus, Nipah virus.	Viral fusion protein, attachment glycoprotein and matrix protein	Development of common Band T cell epitope-based peptide vaccine candidate	(78)
3	Rahman U, et al. 2019	Pakistan, China	Alkhurmahemorrhagic fever virus	Envelope glycoprotein	Identification of potential Band T cell epitopes and development of peptide based vaccine model	(79)
4	Dash R, et al. 2017	Malaysia, Bangladesh	Ebola virus	Viral glycoprotein	B and T cell based epitope-based peptide vaccine	(80)
5	Anwar S, et al. 2020	Canada, USA, Bangladesh	Chikungunya virus	Envelope glycoprotein	Prediction of potential common B cell and T cell epitopes	(81)
6	Verma S, et al. 2018	India	*Salmonella typhi* bacteria	Chaperone protein DnaK	Identification of promising immunogenic B and T cell epitopes.	(82)
7	Unni PA, et al. 2019	India	*Mycoplasma pneumonia* bacteria	Membrane associated proteins and cyt adherence proteins	Prediction of best T cell and B cell epitopes	(83)
8	Zahroh H, et al. 2016	Indonesia	Meningitis-inducing Bacteria (*Streptococcus pneumoniae, Haemophilus influenzae* Type band *Neisseria meningitides*)	Protein of polysaccharide capsule	T cell epitopes based peptide constructs for vaccine	(84)
9	Shahsavandi S, et al. 2015	Iran	Influenza virus	Hemokinin-1 (HK-1) peptide	Identification of conserver T cell epitopes for chimeric vaccine development	(85)
10	Adhikari UK, et al. 2018	Australia, Bangladesh	Oropouche virus	Viral membrane polyprotein	Prediction of common T cell and B cell epitopes for epitope-based peptide vaccine design	(86)

strengthened the immunoinformatics knowledge about the disease pathogenesis of the pathogenic organism. Studies have also provided evidence to understand the immune system dynamics, as well as provided information for *in silico* based vaccine designing. To understand the complex pathogenic process of different pathogenic diseases, computational methods and models were generated for different pathogens such as viral pathogens, bacterial pathogens, parasitic pathogens as well as fungal pathogens. Mirza MU, et al. performed the immunoinformatics analysis along with MD (molecular dynamics) simulations to understand and analyze the different antigenic epitopes of the Zika virus (43). Khan M, et al. have applied an immunoinformatic approach to develop the B and T cell multi-epitope subunit vaccine *for Helicobacter pylori* (44).

Similarly, Urrutia-Baca VH, et al. have tried to develop an oral vaccine against *H. pylori* using novel peptides through immunoinformatics (45). Pandey RK, et al. have designed a multi-epitope-based subunit vaccine against the malarial pathogen (*genus Plasmodium*) using immunoinformatics (46). Rujirawat T, et al. used immunoinformatics and other approaches to understand the oomycete genome of *Pythium insidiosum* (47). Several other examples are available in this direction and provide the utility of immunoinformatics in disease pathogenesis.

8. T Cell and B Cell Epitopes Identification and Characterization for Vaccine Designing Against SARS-CoV-2

The outbreak of the SARS-CoV-2 occurred in China. This disease subsequently spread throughout the world and

Table 3. Different immunoinformatics studies related to T cell and B cell epitopes identification and characterization for vaccine designing against SARS-CoV-2

Sl. no	Researcher group	Country of origin	Identified SARS-CoV-2 protein	Remarks	Reference
1	Sarkar B, et al. 2020	Bangladesh	Surface glycoprotein, Nucleocapsid phosphoprotein	Prediction of common epitopes and antigenicity of B cell and T cell.	(48)
2	Kalita P, et al. 2020	India	Membrane glycoprotein, Surface spike glycoprotein, Nucleocapsid protein	Multi-epitopic (B cell and T cell) peptide identification and antigenicity prediction.	(49)
3	Grifoni A, et al. 2020	USA	ORF3a protein, ORF1ab protein, Surface glycoprotein, Nucleocapsid phosphoprotein, Membrane glycoprotein	Prediction of common epitopes of B cell and T cell.	(50)
4	Bhattacharya M, et al. 2020	India, South Korea	Spike protein	Common epitopes identification of B cell and T cell, antigenicity prediction of T cell	(51)
5	Baruah and Bose, 2020	India	Surface glycoprotein	Prediction of common epitopes and antigenicity of B cell and T cell	(52)
6	Ahmed SF, et al. 2020	China	Nucleocapsid phosphoprotein, Surface glycoprotein	Prediction of common epitopes of B cell and T cell	(53)
7	Kumar S, et al. 2020	India	Spike protein	Epitope identification and antigenicity prediction of T cell	(54)
8	Panda PK, et al. 2020	Sweden, India, Denmark	Spike protein and Mpro	Identification of B cell and T cell epitopes	(55)
9	Bhattacharya M, et al. 2020	South Korea, India	Spike protein	In silico cloning and validation of peptide vaccine candidate	(56)

created a pandemic situation (10). Scientists are desperately trying to develop a vaccine against SARS-CoV-2. Presently, several researchers are using immunoinformatics approaches for the T cell and B cell epitopes identification and characterization as well as vaccine development against SARS-CoV-2. Different *in silico* studies have been performed in recent times to determine the epitopes of SARS-CoV-2. A list of epitopes that have been detected using T and B cells are listed in Table 3.

Recently, Sarkar B, et al. performed epitope-based subunit vaccine development against the SARS-CoV-2 using the immunoinformatics approaches and reverse vaccinology. The research group also performed in silico codon adaptation and MD simulation in this study (48). Kalita P, et al. have also tried to develop a subunit vaccine against SARS-CoV-2. They proposed a multi-peptide-based subunit vaccine through computational biology. The researchers are utilizing T-cell and B-cell epitopes database to identified T-cell and B-cell epitopes, which are then joined through a peptide linker to form a multi-epitopic peptide vaccine (49). Grifoni A, et al. have used immunoinformatics tools and techniques to design a multi-epitopic vaccine. They have predicted common epitopes from the B cells and T cells, and these potential epitopes may be useful to develop human immune responses. In this study, they have used a server titled IEDB server for designing the vaccine. Simultaneously, they have performed the sequence homology to understand the sequence similarity of SARS-CoV-2 with other CoVs (50). In another important study, Bhattacharya M, et al. developed an immunoinformatics based SARS-CoV-2 vaccine using spike protein. They have chosen 13 MHC- I and 3 MHC-II epitopes. These peptides were linked with an (EAAAK)3 linker to develop the multi-epitopic based peptide vaccine for COVID-19. The peptide vaccine was finally docked with the Toll like receptor (TLR) to understand its feasibility to develop adaptive immunity. This rapid immunoinformatics study can be a useful vaccine developmental approach for future researchers (51). Alike, Baruah and Bose have identified the T cell and B cell epitopes for the development vaccine against SARS-CoV-2 though immunoinformatics. In this study, surface glycoprotein was used for the epitopic identification of the COVID-19 vaccine. The study predicted common B cell and T cell epitopes, and their antigenicity was analyzed. They have identified 3 sequential and 5 discontinuous B cell epitopes. The study also characterized the B cell and T cell epitopes and found the existence of salt bridge anchors and continuous hydrogen bonds. Finally, the authors concluded that the vaccine candidate might generate constant humoral immunity in the host (52). Ahmed SF, et al. performed immunoinformatics analysis to developed vaccines against SARS-CoV-2. The study used surface glycoprotein of SARS-CoV-2 and predicted the common epitopes of B cell and T cell. Here,

researchers have mapped the residues of the discontinuous epitopes and linear epitopes of B cells. All these B cell and T cell epitopes sets were found to induce sufficient immune response against SARS-CoV-2 (53). Another study performed by Kumar S, et al. through immunoinformatics using SARS-CoV-2 showed the antigenic variation of S glycoprotein. The study has predicted Cytotoxic T lymphocyte (CTL) epitopes using NetCTL and mIEDB resources. This study also predicted the glycosylation pattern of S glycoprotein (54). Panda PK, et al. performed an extensive study using immunoinformatics to identify the epitopes from spike protein and Mpro. They utilized VixiJen server and found that both the spike proteins (structural protein) and Mpro (nonstructural protein) are antigenic in nature and possess antigenicity. They have identified several T cell and B cell epitopes. From B cell epitopes, they have found both the discontinuous epitopes and linear epitopes (55). In another research by (56) molecular cloning of the identified vaccine construct was reported. The study evaluated various safety measures and the effectiveness of their proposed epitopic vaccine candidate. Even the response of the adaptive immune system was assessed in terms of binding with TLR proteins. Researchers also performed the MD simulation and other characterization to understand the stability, physicochemical and biochemical properties of the vaccine candidate.

Conclusion

In the current scenario, there is an urgent need for the generation of more immunological data related to COVID-19 infection. Immunoinformatics can help to generate immunological data associated with COVID-19 at a faster pace. It has been observed that most of the studies that are performed for COVID-19 using immunoinformatics are focused on B and T cells epitopes identification and characterization. Basically, B cells and T cells are two significant components that can elicit an immune system to fight against all pathogens, including viruses. For the body's defense mechanism, activation of these two cell types plays a crucial role. Moreover, the activation of adaptive immunity is a prerequisite for the development of body defense after vaccination. All literatures reviewed for the immunoinformatics on epitope identifications will help to develop a significant vaccine against SARS-CoV-2. Soon, we can expect to utilize these rapidly generated databases for developing effective peptide vaccine against COVID-19 and help to protect the diverse human population.

Ethics Approval and Consent to Participate

Not applicable

Informed consent and patient details

Not required.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.01.004.

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