A web-based platform on COVID-19 to maintain Predicted Diagnostic, Drug and Vaccine candidates

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Abstract

A web-based resource CoronaVIR (<https://webs.iiitd.edu.in/raghava/coronavir/>) has been developed to maintain predicted and existing information on coronavirus SARS-CoV-2. We have integrated multiple modules including “Genomics”, “Diagnosis”, “Immunotherapy” and “Drug Designing” to understand the holistic view of this pandemic medical disaster. Genomics module provides genomic information of different strains of this virus to understand genomic level alterations. The Diagnosis module provides detailed information on currently-in-use diagnostics tests as well as on five novel universal primers-sets predicted using in silico tools. The Immunotherapy module provides information on epitope-based potential vaccine candidates (e.g., LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPPTEPKKDKKKK, EITVATSRTLS, GKGQQQQGQTV, SELVIGAVILR) predicted using state-of-the-art software and resources in the field of immune-informatic. These epitopes have potential to activate both adaptive (e.g., B-cell, T-cell) and innate (e.g., vaccine adjuvants) immune systems as well suitable for all strains of SARS-CoV-2. Besides, we have also predicted potential candidates for siRNA-based therapy and RNA based vaccine adjuvants. Drug Designing module maintains information about potential drug targets, tertiary structures and potential drug molecules. These potential drug molecules were identified from FDA approved drugs using the docking-based approach. We also compiled information from the literature and the Internet on potential drugs, repurposing drugs and monoclonal antibodies. To understand host-virus interaction, we identified cell-penetrating peptides in the virus. In this study, state-of-the-art techniques have been used for predicting the potential candidates for diagnostics and therapeutics.

Keywords: COVID-19; SARS-COV-2; 2019-nCoV; Resource; Corona; Vaccine; Drug; Diagnosis; Bioinformatics; Prediction

Introduction:

The year 2019 ended with the outbreak of a new disease called pneumonia of an unknown cause that occurred in China (1). Several independent laboratories identified the causative agent of this enigmatic pneumonia as a novel coronavirus, which has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease caused by this has been named as coronavirus disease-19 (COVID-19) (2–4) The World Health Organization (WHO) has declared this outbreak as pandemic because the virus has spread across the globe

and infected thousands of people within months of its emergence. As of April 3, 2020, more than 1 million people are reported as infected with COVID-19. With this high rate of increase of this infection, the damage has reached an alarming number of more than 54,000 deaths, with more than 14,000 deaths in Italy alone (5). SARS-CoV-2 belongs to a family of coronaviruses, which are highly diverse, enveloped, positive-sense, single-stranded RNA viruses (6). It shares a 79.5% sequence identity with SARS-CoV-1 and 96.2% identity with bat CoV RaTG13 (7). The phylogenetic analysis indicates that SARS-CoV-2 belongs to subgenus *Sarbecovirus* of the genus *Betacoronavirus* and is distinct from SARS-CoV-1 (2–4). SARS-CoV-2 is a new strain of coronavirus which is the seventh member of the family of coronaviruses to infect humans, after MERS-CoV and SARS-CoV-1. It has been shown in recent studies that this new strain uses the same cell receptor, i.e. angiotensin-converting enzyme 2 (ACE2) for the entry into the host cell as used by earlier strains of coronavirus (8). Yushun Wan et al suggested that the single N501T mutation in Spike protein of SARS-CoV-2's probably significantly enhanced its binding affinity for ACE2 (9). The exact mechanism of action for SARS-CoV-2 is still needed to be discovered (10).

Due to the pandemic nature of the COVID-19 outbreak and the increase in global incidences, consistent efforts are going on to contain the situation and manage the infected patients. While there has been an exponential rise in the research studies, no effective treatment or vaccine is yet available for COVID-19. However, several clinical trials have been proposed or are undergoing (11). The majority of these trials are being conducted all over the world, for instance, the two largest trials are GDCT0379047 (ChiCTR2000029573) and GDCT0379500 (ChiCTR2000029602) (12). A clinical trial to evaluate the efficacy of the antiviral 'Remdesivir' has also begun in the US by NIH (13). Apart from these, various standard therapies such as antipyretic therapy, oxygen therapy, renal replacement therapy (RRT), and drugs related to SARS such as Oseltamivir, the combination of IFN- α and lopinavir/ritonavir are in current clinical use for managing infected patients (14). It is also crucial to note that the current progress in the coronavirus vaccine research wouldn't have been possible without the endeavor of clinical bioinformaticians working behind closed doors. With the elucidation of the SARS-CoV-2 biological sequence, there have been numerous attempts to understand the virus at the molecular scale, which has led to the development of various in-silico tools and resources notably (15). Various online dashboards were developed by the researchers such as at John Hopkins CSSE, which can be further used to track the COVID-19 cases in real-time and also for other important statistics (16).

An individual researcher or research group or even a single institute has insufficient resources and knowledge to provide a time-bound solution against a pandemic (e.g., COVID-19). To provide effective solutions against a deadly disease in limited time, one should generate and promote open-source resources. These resources can be used by experimental researchers and clinicians to provide ultimate solutions against any epidemic or pandemic. In this study, we developed a platform that offers computer-aided solutions to manage COVID-19. These resources are generated using state-of-the-art techniques in the field of bioinformatics. These computer-aided solutions include primers for diagnosis, molecules for therapeutic (drugs & vaccine). In order to provide complete and comprehensive information, we also compile information from the literature and the Internet. To facilitate the scientific community against this deadly disease COVID-19, we provide a web-based platform.

Material and Methods

General Information

There is a variety of relevant information regarding SARS-CoV-2 virus and its resulting disease COVID-19. This information is scattered in different forms like literature, web-resources, and databases. We performed keyword search on google search engine using different terms relevant to SARS-CoV-2 and COVID-19. We manually evaluate these links obtained from google search to identify authenticated information. Finally, important and authenticated links, videos and documents were compiled and integrated into CoronaVIR.

Genomic and proteomic data collection

The whole genome and proteome sequences of SARS-CoV-2 were retrieved from the NCBI. We have obtained 53 genome sequences of SARS-CoV-2 strains from NCBI (17). Besides, a total of 10 protein sequences of the Wuhan genome (Accession ID MN908947.3) were extracted till February 2020.

Diagnosis

Firstly, PubMed and Google search engines were mined using keywords like “2019-nCoV Diagnosis”, “Diagnostic Primers”, “2019-nCoV” and “COVID-19”, etc. This information was used to identify 12 diagnostic assays and primers (primer combinations) from four publications; reported till March 1, 2020. Secondly, we downloaded 53 complete genomes (Accession ID with other information like strain and source country given in Table S1 (Supplementary Material) and 40 nucleotide sequences of the 5 genes (N, E, M, ORF1ab, ORF1ab-RdRP) of COVID-19 from the NCBI Virus Resource (18) on March 10, 2020. Thirdly, we designed primers corresponding to whole-genome and specific genes using the

Primer3_core tool (19, 20) with default parameters. Notably, we have generated primers for each of the sequences individually in case there are multiple sequences present for any of the genes. Subsequently, we removed duplicate primer pairs for each of the sequences or genes. In addition, we also compiled the diagnostic primers of other strains of coronavirus from the MRPrimerV (21), a public database of primers for viruses. Besides, we have also collected and compiled the information regarding the various diagnostic tests for COVID-19 from the literature.

Vaccine Design

To identify potential peptides that could serve as vaccine candidates, we generate all possible 9-mer peptides from different proteins of SARS-CoV-2 (Accession No MN908947). A wide range of immune-informatics tools have been used to predict B-cell epitopes, T-cell-epitopes, MHC binders, and vaccine adjuvants.

B-cell epitopes: In this study, LBtope (22) has been used to predict B-cell epitopes from the above 9-mer peptides of the different proteins of SARS-CoV-2. LBtope is a highly efficient method that is built and trained on the vast dataset of B-cell epitopes and non-epitopes that were experimentally validated, implemented in numerous studies (23–27). The prediction was made with the default threshold of 60% cut-off, which was also previously used by Gupta et. al. for designing epitopes for the Zika virus (28).

T-cell epitopes: To predict Cytotoxic T lymphocytes (CTL), we used the immune-informatics tool CTLPred (28). It is a direct method which is based on the primary sequence of the antigens for predicting the CTL epitopes rather than predicting the MHC class I binders. It has implemented machine learning techniques such as artificial neural network (ANN) and support vector machine (SVM). In this work, CTL epitopes were predicted using ANN module of the CTLpred with the default parameters and with the cut-off score of 0.51.

Promiscuous MHC binders: The major histocompatibility complex (MHC) plays a key role in the human immune system. It expresses on the cell surface and binds to the antigenic peptides. Subsequently, it presents the peptide to activate the T-cells. In this study, potential MHC Class I and Class II binders identified using ProPred 1 (28) and ProPred (28), respectively. The prediction was done with the default parameters, i.e., 4% threshold for ProPred 1 to predict MHC Class I binders and 3% threshold for ProPred for predicting MHC Class II binders. We identified promiscuous MHC binders that can bind to large number MHC alleles.

Experimentally validated epitopes: The Immune Epitope Database (IEDB) (28) is the repository that contains a significant number of experimentally validated epitopes or

antigenic regions that tend to modulate the immune system. Therefore, with an aim to identify only those epitopes of SARS-CoV-2 that have already been characterized in the past, we have mapped the epitopes predicted in our study with the experimentally proven IEDB epitopes. To further narrow down the search, we have used the different filters i.e., coronavirus as source organisms and coronavirus protein as antigen name to extract the epitopes.

Vaccine Adjuvants: We have used VaxinPAD (28) to identify the potential peptide-based vaccine adjuvants. It is used to predict the immuno-modulatory peptides or Antigen-presenting cell epitopes (A-cell epitopes). For determining the potential peptide-based vaccine adjuvants, we have used the SVM based model with the threshold of -0.5. In addition to peptide-based vaccine adjuvants, we predicted nucleotide-based vaccine adjuvants from genes of 10 proteins (see Table S2, Supplementary Material) of SARS-COV-2 (Accession ID MN908947). In this study, we used the “Batch mode” of VaccineDA with default parameters (28); the length of adjuvants is 30 nucleotides.

RNA therapeutics

With an aim to design siRNA-based therapeutics against the SARS-CoV-2 strain, we generated 19mer oligonucleotide from the corresponding mRNA sequences (Accession ID MN908947), as this length is considered to be sufficient to silence the cognate mRNA target sequence. Previously, many of the prediction methods were developed based on the 19mer length of siRNA sequence (29–32). To identify which siRNA oligonucleotide could serve as an efficient siRNA against the SARS-CoV-2, we predicted the efficacy of each of oligonucleotides (siRNA) using “DesiRm” software with default parameters (32). Eventually, we have extracted the highly potent siRNAs (having efficacy greater than 0.80 value) and target accessibility of 0.60.

Drug Designing

In this platform, we integrated the “Drug Designing” module, which elucidates various aspects related to the designing of potential drug candidates for the treatment of COVID-19. Here, mainly four sub-modules have been implemented viz. potential drug target, 3D-structure, potential drug molecule, and cell-penetrating peptides.

Potential Drug targets: This sub-module provides details about potential drug targets that could be used for designing drugs. As this new strain, i.e. SARS-CoV-2 shares high sequence similarity (up to 96%) with the previous strains i.e. MERS, SARS, Bat-SARS coronavirus (2, 33, 34), chances of having the same drug targets is higher. Therefore, based on literature searching and previous studies (2, 34), we have provided the details of some of the probable

drug targets such as target name, sequence, locus tag, etc. This complete information was extracted from the complete reference genome sequence of Wuhan Coronavirus (Accession ID: NC_045512.2).

Tertiary structure: One of the pre-requisites for designing drugs is the availability of tertiary or three-dimension (3D) structures of drug targets. SARS-CoV-2 encodes a number of proteins that could act as potential drug targets; however, 3D structures of only selective proteins such as spike glycoprotein (PDB ID: 6VSB), and nucleocapsid phosphoprotein (PDB ID: 6VYO) are available in the Protein Data Bank (PDB). We predict the 3D structures of the SARS-CoV-2 proteins using Phyre 2.0 server (7). Towards this, protein sequences were extracted for the complete genome of SARS-CoV-2 (NCBI reference NC_045512.2) from NCBI. Phyre 2.0 is a homology-based software for predicting the 3D structure of a protein. Default parameters were used while predicting the structures except for modeling mode which was set to intensive instead of normal. The quality assessment of the predicted structures was performed using PROCHECK (35, 36), and QMEAN software (37). These structures can be used for docking studies for designing new inhibitors.

Potential Drug Molecule: An extensive search was performed in different databases like Pubmed, DrugBank (38–40) to identify potential drugs. As there is no FDA approved drug specific to COVID-19 till today, we look for the drugs which have already been approved for the viruses similar to SARS-CoV-2 such as SARS, MERS, etc. The logic behind this approach was based on the similarity of the genomic layout, and the cellular and molecular biology of these viruses.

In addition, we used the PatchDock server (41, 42) for docking the putative drug molecules to their targets. The parameters used for docking were “clustering RMSD” as 4.0 and “complex type” as the protein-small ligand. Modeled protein-drug structures were further analyzed using PyMOL software (43).

Cell-Penetrating Peptides: It is important to identify cell-penetrating peptides in SARS-CoV-2 proteins to understand the mechanism of host-virus interaction. Cell-penetrating peptides in viral proteins help virus to enter into the cell of host. In addition, cell-penetrating peptides can be used for drug delivery. In the past, most of the cell-penetrating peptides were discovered from viral proteins, for example widely used TAT peptides discovered from HIV (44, 45). Here, we used CellPPD (46) to predict the cell penetrating peptides in SARS-CoV-2; each peptide has 10 amino acids. Different physicochemical properties such as hydrophobicity, charge, molecular weight, etc. of the peptides were also computed. Based on the SVM scores, we selected the top 10 CPPs from different viral proteins, which could be

used as vehicles for drug delivery. The higher the SVM score, the more likely the peptide is to be a CPP.

Webserver Implementation

CoronaVIR has been developed using HTML, PHP 5.2.9, and JAVA scripts. A responsive website based on HTML5 has been used to make the website compatible with mobiles and tablets.

Results

General Information

In the current study, we have developed a comprehensive web-based resource named as “CoronaVIR” for SARS-CoV 2 or COVID-19. As shown in Figure 1, information has been organized into five modules or categories. First, the module provides general information about this virus and disease. Here we collected and compiled vital information from a wide range of resources including literature. In addition, we have used various in-silico techniques to identify potential diagnostic primers, peptide-based vaccine candidates and potential drug molecules. The overall architecture of the resource is shown in Figure 1. Each of the sections described below in detail.

Figure 1: The overall architecture of the CoronaVIR.

Genomics Module

The 53 genome sequences of SARS-CoV-2 strains were submitted by different groups from various regions worldwide. It includes 25 from China, 19 from the USA, two each from India and Taiwan (Table S1). In order to facilitate community, we have provided comprehensive information on these genomes that includes strain name, size and, Accession ID. In addition, the original source like NCBI resource has been linked. Ten protein sequences were manually checked for the presence and absence of well-reported ORFs, and thereafter categorized. These ten proteins include Orf1ab polyprotein, Orf3a protein, Envelope protein (E), Orf6 protein, Orf7a protein, Orf8a protein, Orf10 protein, spike protein. We have also provided the important links or URLs of NCBI virus genomic resources on the webserver to obtain the latest and updated information regarding genomes.

Diagnosis Module

Diagnostic Primers: This section provides information about 12 experimentally validated primer pairs collected from the literature. In addition, this section also contains information about 65 unique predicted primers pairs. Following is distribution of these predicted primers; i) five pairs for complete genome, ii) 20 for N-gene & ORF1ab-RdRP, iii) 10 for ORF1ab and iv) five each for M-gene and E-gene of COVID-19. We named five pairs of primers, which designated from the complete genome as “Universal primers” as they are found to be common among all the 53 different genome sequences, shown in Table 1. In the case of experimentally validated primers, we have provided the gene symbol of the gene against which primers designated, sequences, T_m, and GC content (%) of forward (Fwd) primers, reverse (Rev) primers and probes (oligo). Experimental assay conditions like T_m, Concentration, etc. are also provided along with the reference study, specific comments regarding their experimental condition or result inference, from the respective study. In case of predicted primers, we have provided information like nucleotide sequences, T_m, and GC content (%) of the forward (Fwd) primers, reverse (Rev) primers and probes (oligo). Besides, we have also provided information like the ID and country of source sequence, with gene symbols. Further, we have also compiled information (e.g., sequences, T_m, GC contents, quality score) for 296 primer pairs for other strains of the coronavirus, obtained from the “MRPrimerV”. The detailed information related to all primer sets can be found on the “Diagnostic Primers” sub-module under the “Diagnosis” module on the webserver (<https://webs.iiitd.edu.in/raghava/coronavir/prim.php>).

Diagnostic Tests: This section provides the detailed information of all the possible diagnostic tests which can be carried out for the diagnosis of COVID-19. Besides, this

module provides guidelines for its collection and storage and the procedure to perform diagnosis via RT-PCR assay, which is the most common diagnostic test used under the current scenario. All the specified information is collected from the recent literature. To facilitate the users, we have also provided the detailed documentation on this on the webserver (<https://webs.iiitd.edu.in/raghava/coronavir/diag1.php>).

Table 1: Potential candidates for Universal Diagnostic primers sets for COVID-19 (predicted using Primer3_core), which are common among 53 different Genome sequences (obtained from NCBI Virus Resource).

Fwd seq	Rev seq	Oligo	Fwd Tm	Rev Tm	Oligo Tm	Fwd GC	Rev (GC)	Oligo GC	Target size
CTCTTCTCGTT CCTCATCACG	CCAGACATTTT GCTCTCAAGC	TTGCTGCTG CTTGACAG ATT	59.99	60.01	59.75	52.38	47.62	45	162
AGTCAAGCCT CTTCTCGTTC C	CCAGACATTTT GCTCTCAAGC	TTGCTGCTG CTTGACAG ATT	60.01	60.01	59.75	52.38	47.62	45	170
GTCAAGCCTC TTCTCGTTCCT	CCAGACATTTT GCTCTCAAGC	TTGCTGCTG CTTGACAG ATT	60.01	60.01	59.75	52.38	47.62	45	169
AGCCTCTTCT CGTTCCTCAT C	CCAGACATTTT GCTCTCAAGC	TTGCTGCTG CTTGACAG ATT	59.97	60.01	59.75	52.38	47.62	45	165
GGGGGACAA CCAATCACTA AT	TAACCTTTCCA CATACCGCAG	CAGTTACAC CGGAAGCC AAT	59.93	60.01	59.99	47.62	47.62	50	278

Fwd: Forward Primer; Rev: Reverse Primers; seq: sequence; Tm: Melting Temperature, GC: GC content (%age)

Immunotherapy or Vaccine Design Module

Peptide-based therapeutics

In the current study, we have predicted potential coronavirus epitopes which include B-cell epitopes, T-cell epitopes, and MHC class I and class II binders. A total of 594 B-cell epitopes and 966 T-cell epitopes predicted, which have $\geq 60\%$ probability of correct prediction, are

shown on the website with their peptide sequences. Additionally, 31,215 MHC class I and 17,635 MHC class II binders were predicted using ProPred 1 and ProPred, respectively, and are displayed on the website. Apart from that, 117 experimentally validated IEDB epitopes were mapped to corona antigens, which include B-cell and T-cell assays. The information about assay include PubMed ID, epitope description, host organism, technique used, assay group, and qualitative measure.

Potential Vaccine Candidates: In this study, we have suggested 17 epitopes that can act as potential vaccine candidates against SARS-CoV-2 based on the results of different prediction methods. The epitopes which were conserved among different prediction tools such as LBtope, CTLPred, VaxinPAD, ProPred 1, and ProPred as well as experimentally validated by IEDB, were chosen as potential vaccine candidates, as shown in Table 2. Besides, we have linked these epitopes on our webserver, “CoronaVIR” to the source page of IEDB (<https://webs.iitd.edu.in/raghava/coronavir/map.php>). Further, by clicking on ID, user can get complete information regarding the epitope, organism, antigen, assays used, etc. Out of these 17 vaccine candidates, five epitopes, i.e. LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPTEPKKDKKKK, EITVATSRTL, GKGQQQQGQTV, and SELVIGAVILR are reported in IEDB (B-cell, and T-cell assays), LBtope, CTLPred, VaxinPAD, ProPred, and Propred 1.

Table 2: Potential Vaccine Candidates include IEDB (B-cell and T-cell assay), B-cell epitope, T-cell epitope, Vaccine Adjuvants, MHC class I and II binders.

Protein	Potential Vaccine Candidate	IEDB (T-cell) (#1)	IEDB (B-cell) (#1)	B-cell epitope (#2)	T-cell epitope (#3)	Vaccine Adjuvants (#4)	MHC-I (#5)	MHC-II (#6)
Nucleocapsid Phosphoprotein	LQLPQGTTLPKGFYA	✓	✓	✓	✓	✗	✓	✓
Nucleocapsid Phosphoprotein	VILLNKHIDAYKTFPTEPKKDKKKK	✓	✓	✓	✓	✗	✓	✓
Membrane Glycoprotein	EITVATSRTL	✓	✓	✓	✓	✗	✓	✓
Nucleocapsid Phosphoprotein	GKGQQQQGQTV	✓	✓	✓	✓	✗	✓	✗

Membrane Glycoprotein	SELVIGAVILR	X	✓	✓	✓	✓	✓	✓
Envelope Protein	ALRLCAYCCN	✓	X	✓	✓	✓	✓	✓
ORF6	HLVDFQVTIAEILLIIMR	✓	X	✓	✓	X	✓	✓
Envelope Protein	VFLLVTLAILTALRLCAYCCNI	✓	X	✓	✓	✓	✓	✓
Membrane Glycoprotein	NGTITVEELKKLLEQWNLVIGFLFL	✓	X	✓	✓	✓	✓	✓
Membrane Glycoprotein	ASFRLFARTRSMWSFNPETNILLNVPLHGT	✓	X	X	✓	✓	✓	✓
Membrane Glycoprotein	SRYRIGNYKL	✓	X	X	✓	✓	✓	✓
ORF8	RCSFYEDFLEYHDVR	X	X	✓	✓	✓	✓	✓
ORF6	IWNLDYIINLIKNLSKSLT	X	X	✓	✓	X	✓	✓
Surface Glycoprotein	SETKCTLKSFTVEKGIYQTSNF	X	X	✓	✓	X	✓	✓
ORF8	MKFLVFLGIITTVAAFHQECSLQSCTQ	X	X	✓	✓	X	✓	✓
ORF3a	DGTTSPISE	X	X	✓	✓	X	✓	X
ORF3a	SKIITLKKRWQLALSKGVHFVCNLLL	X	X	✓	✓	✓	✓	X

293 #1: IEDB, #2: LBtope, #3: CTLPred, #4: VaxinPAD, #5: ProPred 1, #6: ProPred

294 Mapping and Validation of Predicted Epitopes in strains of various Countries

295 Next, we aimed to validate our peptide-based potential vaccine candidates in other strains
296 across the globe. Towards this, we have randomly taken six different genomes from different

countries available for SARS-COV-2 strains from NCBI with Accession IDs MT012098, MT050493, MT066156, MT159711, MT246462, and MT233519. Subsequently, we mapped our top five peptide-based vaccine candidates. Mapping results showed that these epitopes are present in all these strains, shown in Table 3. These results indicate that these vaccine candidates can be implemented widely across the globe.

Table 3: Mapping and Validation of predicted Epitopes in SARS-COV-2 strains from other parts of Globe.

Epitope	Protein	Accession IDs and Country					
-	-	MT012098	MT050493	MT066156	MT159711	MT246462	MT233519
-	-	India	India	Italy	USA	USA	Spain
LQLPQGTTLPKGFYA	Nucleocapsid Phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
VILLNKHIDAYKTFFP TEPKDKKKK	Nucleocapsid Phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
EITVATSRTLS	Membrane Glycoprotein	Yes	Yes	Yes	Yes	Yes	Yes
GKGQQQQGQTV	Nucleocapsid Phosphoprotein	Yes	Yes	Yes	Yes	Yes	Yes
SELVIGAVILR	Membrane Glycoprotein	Yes	Yes	Yes	Yes	Yes	Yes

Nucleotide-based adjuvants: First, we predicted a large numbers of nucleotide-based vaccine adjuvants for each of ten proteins using VaccineDA, as given in Table S2 and on the webserver (<https://webs.iitd.edu.in/raghava/coronavir/adj.php>). Subsequently, top ten potential vaccine adjuvants candidates selected based on the SVM-score, enlisted in Table 4. Out of them, oligodeoxynucleotide of Orf8 and Orf1ab, i.e. “GCGTTGTTTCGTTCTATGAAGACTTTTTAGA” and “ACGTTAATACGTTTTTCATCAACTTTTAACG” withstand to be exceptionally immunomodulator with the SVM score of 1.885 and 1.537, respectively.

Table 4: List of potential nucleotide-based vaccine adjuvants, predicted by the VaccineDA for the 10 proteins from SARS-CoV-2.

Protein name	Sequence	SVM Score	Length	Mol. Wt.	Tm	GC content (%)
Orf8	GCGTTGTTTCGTTCTATGAA GACTTTTTAGA	1.885	30	9233.09	57.52	36.67
Orf1ab	ACGTTAATACGTTTTTCATC AACTTTTAACG	1.537	30	9130.04	54.79	30
Envelope protein	ACGTTAATAGTTAATAGC GTACTTCTTTTT	1.492	30	9176.08	53.42	26.67
Orf6	ATTATGAGGACTTTTAAA GTTTCCATTGG	1.33	30	9241.12	54.79	30
Surface glycoprotein	ACTAATGTCTATGCAGAT TCATTTGTAATT	1.265	30	9185.09	53.42	26.67
Orf3a	TTCTCTATCTTTATGCTTT AGTCTACTTCT	1.248	30	9044.96	54.79	30
Nucleocapsid glycoprotein	GCGTTGTTTCGTTCTATGAA GACTTTTTAGA	1.085	30	9246.08	61.62	46.67
Membrane glycoprotein	TAACTTTAGCTTGTTTTGT GCTTGCTGCTG	1.068	30	9191.04	58.89	40
Orf7a	CTCTAGCTGATAACAAAT TTGCACTGACTT	0.797	30	9140.03	57.52	36.67
Orf10	AACGTTTTTCGCTTTTCCGT TTACGATATAT	0.796	30	9128.02	56.15	33.33

316

317 RNA therapeutics

318 This section maintains a list of potential siRNAs that can serve as candidates for RNA based
319 therapeutics. As shown in Table 5, these siRNAs can suppress or degrade different genes of
320 SARS-CoV-2 with high efficacy (>0.80); each siRNA has high target accessibility (>0.6).
321 Here, we have shown only the top 10 siRNA that can serve as a therapeutic candidate against
322 COVID-19. Among them, Orf1ab protein is shown to be the top protein with the predicted
323 antisense sequence of siRNA “AAAUUGAUCGUACAACACG” and mRNA target
324 sequence “CGUGUUGUACGAUCAAUUU” with target accessibility of 0.636979 and
325 efficacy of 1.129115.

326 **Table 5: List of the top 10 oligo-nucleotide candidates that could serve as efficient**
327 **siRNA against COVID-19.**

Protein name	Antisense Sequences of siRNA	Position on mRNA	mRNA target sequence	Target accessibility	Efficacy
Orf1ab protein	AAAUUGAUCGUACA ACACG	12	CGUGUUGUACGAUCA AUUU	0.637	1.129
Orf3a protein	AACAACAACAGCAA GUUGC	11	GCAACUUGCUGUUGU UGUU	0.979	1.080
Surface protein	UAAGAUUAACACAC UGACU	3	AGUCAGUGUGUAAU CUUA	0.722	1.078
Envelope protein	UUAACUAUUAACGU ACCUG	10	CAGGUACGUUAAUAG UUAA	0.768	1.053
Orf6 protein	UUUAUUCUCAGUUA GUGAC	12	GUCACUACUGAGAA UAAA	0.654	1.034
Nucleocapsid protein	UUUGUAUGCGUCAA UAUGC	8	GCAUAUUGACGCAUAC AAA	0.676	1.033
Membrane protein	AAACAAGCUAAAGU UACUG	3	CAGUAACUUUAGCUU GUUU	0.673	1.010
Orf10 protein	UAACUACAUCUACU UGUGC	4	GCACAAGUAGAUGUA GUUA	0.723	0.981
Orf8 protein	UGAUACUCUAAAAA GUCUU	3	AAGACUUUUUAGAGU AUCA	0.947	0.923
Orf7a protein	AAAUUGAGUGCUAA AGCAA	11	UUGCUUUAGCACUCAA UUU	0.791	0.819

328

329 **Drug Designing Module**

330 **Drug Targets:** In previous studies, it has been shown that some of the potential viral drug
331 targets include non-structural proteins (nsp) (papain-like protease, RNA-dependent RNA
332 polymerase, helicase, etc.), structural proteins (nucleocapsid protein, envelope protein, spike
333 protein) and other accessory proteins (47, 48). As SARS-CoV-2 also has a positive sense
334 single-stranded RNA as its genetic material, therefore, we compiled this information about
335 these targets for SARS-COV-2. Thus, we selected the potential drug targets, which are key
336 components of the COVID-19 infection lifecycle. This includes proteins involved in the viral
337 entry into the host cell, viral replication machinery, and viral RNA synthesis. The

information includes Accession ID, Gene encoding the protein, Locus Tag, Source of the protein, Protein sequence, and identical proteins. All this information can be accessed from the webserver (<https://webs.iiitd.edu.in/raghava/coronavir/dt.php>).

3D Structure: As per RCSB-PDB data till 25 March, more than 90 crystallized structures related to SARS-CoV-2 have been reported (<http://www.rcsb.org/pdb/results/results.do?tabtoshow=Current&qrid=D12523A6&startAt=0&resultsperpage=93>). On our webserver, firstly we maintained structures of some of the important ones include crystallized structures of spike glycoprotein (PDB ID: 6VSB), HR2 domain of 2019-nCoV (PDB ID: 6LVN), post-fusion core of SARS-CoV-2 S2 subunit (PDB ID: 6LXT) and crystal structure of main protease in association with an inhibitor N3 (PDB ID: 6LU7). Besides, Phyre2.0 server (7) was used for modeling the structures of various other proteins. Here, we modeled ten important proteins that include RNA-dependent RNA-polymerase, Envelop Protein, membrane glycoprotein, nucleocapsid phosphoprotein, and ORF3a protein, etc. which could be potential drug targets, as represented at webserver (<https://webs.iiitd.edu.in/raghava/coronavir/struct2.php>). We observed that our modeled structures were of good quality as for most of the protein residues are present in the allowed region (here we consider most favored regions, additional allowed regions and generously allowed regions). Also, the QMEAN score, which is measured in the range of 0-1, was found to be present above 0.5 for most of the residues. Overall, the model is good enough for drug designing studies. Detail information of the structures such as template information, the percent identity of the query sequence with the template sequence, type of fold present in the template, etc. Users can download the structures and the Ramachandran Plot from the link <https://webs.iiitd.edu.in/raghava/coronavir/struct.php>.

Potential Drug Molecules: We mapped the SARS-CoV-2 genome to existing FDA approved drugs present in the DrugBank. This leads to the identification of drugs (e.g., camostat myselate, Ritonavir, Lopinavir, and Remdesivir, Chloroquine) that has potential to treat COVID-19. These drugs have been previously proposed to treat various viral infections (49–53). For example, Kaletra is an approved combination of HIV protease inhibitors ritonavir, and lopinavir is currently under clinical trials for treating COVID-19 infection, and in some patients, it has shown some promising results. Further, we have also performed the docking procedure by docking the putative drugs on the predicted structures of the targets from SARS-CoV-2. To compare our docked structures, we have also docked the drugs with their targets given in Drugbank (38–40), whose structures are available in PDB (REF). We found

that gs-6620, which is similar to Remdesivir, got the highest score among all. Table 6 represents a list of some of the potential drugs along with their target information. We have also compiled the list of a drug which have been predicted computationally or are repurposed drugs from different studies, is provided at our website. Besides, Dong L et al 2020 suggested the five antiviral drugs included in the Guidelines (version 6) for treatment of COVID-19, available on the webserver (11). Users can browse those drugs by clicking on the “Click to view complete file” tab provided at the website <https://webs.iiitd.edu.in/raghava/coronavir/dm.php>.

Table 6. List of potential drugs which could be used for treating COVID-19 infection

S.No.	Drug	FDA-Status	SARS-CoV-2 Receptors	Targets in Drugbank (PDBID)	Patchdock score	
					SARS-CoV-2	Targets in Drugbank
1	GS-6620	Investigational	RDRP	Hepatitis C Virus Ns5b Rna-Dependent Rna Polymerase (1C2P)	8724	7364
2	Cobicistat	Approved	3C-like proteinase	NA	8096	NA
3	Ritonavir	Approved, Investigational	3C-like proteinase	HIV-1 Protease (5V4Y)	7802	8016
4	Remdesivir	Investigational	RDRP	RNA-directed RNA polymerase L (NA)	7554	NA
5	Lopinavir	Approved	3C-like proteinase	HIV-1 Protease (5V4Y)	7512	7894
6	Camostat myselate	Experimental	TMPRSS2	NA	6396	NA
7	Darunavir	Approved	3C-like proteinase	HIV-1 Protease (5V4Y)	5934	7316
8	Fosamprenavir	Approved	3C-like proteinase	HIV-1 Protease (5V4Y)	5934	6754

Drug Delivery: We predicted CPPs corresponding to 10 proteins of the SARS-CoV-2 using CellPPD server. These peptides can be used for drug delivery. In addition, these peptides can be used to understand virus-host interaction. User can also get detailed information like SVM score, physic-chemical properties include hydrophobicity, hydrophilicity, charge, molecular weight, etc. at the website <https://webs.iiitd.edu.in/raghava/coronavir/dd.php>.

Comparison with previous studies

Currently, the quest for effective vaccine design against COVID-19 is increasing among research groups. Similar analyses for vaccine designing are being conducted or already reported in various studies. For instance, a report by Ramaiah A et al. in February 2020, proposed eight CD4 T-cell epitopes in the S, E, M and N proteins based on the Asia and Asia-Pacific Region population using computational approach (55). These epitopes can be recognized by HLA-DR alleles. Besides, recently Ahmed et al also suggested potential vaccine candidates, i.e. a set of B cell and T cell epitopes derived from S and N proteins for SARS-COV-2 based on the analysis of experimentally validated epitopes of SARS-COV having sequence similarity with SARS-COV-2 (56). Furthermore, Marek Prachar et al proposed 174 SARS-CoV-2 epitopes that are in vitro validated to bind stably to 11 HLA allotypes include 10 HLA class I and one HLA class II based on using the computational and in vitro analysis (57). Furthermore, various studies predicted multi-epitopes or numerous vaccine candidates for SARS-COV-2 infections using the computational approach as represented by different pre-prints (58–62). The question arises, why another study for designing an epitope-based vaccine against COVID-19. Best of our knowledge, none of the existing studies identify epitopes that can activate both innate and adaptive immune system. In our study, we identified peptides that can activate both arms of the immune system as well as identify promiscuous MHC binders and vaccine adjuvants. As shown in Table 2, potential peptides identified in this study have almost all required properties for an effective vaccine. Besides, top five vaccine candidates from our study also mapped on six SARS-COV-2 strains from different parts of world. This indicates, their universal utility aspect. Thus, additional features of our vaccine module will complement existing studies in fighting against COVID-19.

Knowing the fact of the importance of drugs in curbing the COVID-19, numerous researchers focused on the elucidation of potent drugs. In this study, we compile these studies to provide information from a single source. Various reports suggested repurposing of different drugs for COVID-19 patients (48, 63, 64). A molecular docking study by Elfiky AA suggested Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir as potent drugs against SARS-CoV-2 as tightly bound to its RdRP (65). Moreover, this study also proposed the IDX-184, Setrobuvir, and YAK as antiviral treatments for COVID-19. Further, an in vitro study by Manli Wang et al showed the effectiveness of Remdesivir and Chloroquine in the controlling the of COVID-19 infection (66). Importantly, a study by Chu CM et al on 41 patients with COVID-19 that were treated with a combination of Lopinavir/Ritonavir and Ribavirin

showed favorable outcome in comparison to the 111 patients treated with Ribavirin only and placebo controls; thus suggested the clinical utility (67). Moreover, one of the studies is focussed on the development of COVID-19 Docking Server (68). This tool predicts the binding modes between COVID-19 targets and the ligands including small molecules, peptide and antibody. Besides, Dong L et al. summarizes the antiviral drugs and their efficacy included in the Guidelines (version 6) for treatment of COVID-19 (11). Inconclusively, all these reports targeted one or other aspect of the various drugs in combating the COVID-19. In our study, we have tried to cover the holistic view of the drug design or available drugs to curb the COVID-19. Therefore, we have predicted drug targets, their structure, compiled possible drug molecules from the literature. Besides, to understand host-virus interaction, we have also predicted CPP from viral proteins. One of our goals is the feasibility of identified candidates for the experimental validation. Therefore, we prioritized these vaccine or drug candidates as a minimum manageable subset. Eventually, it will facilitate the possibility of their implementation in real life.

Discussion and Conclusion

The ongoing severe pandemic outbreak of COVID-19 is the major concern across the globe. Currently, COVID-19 has affected 205 countries and territories with one international conveyance, i.e. the Diamond Princess cruise ship harbored in Yokohama, Japan, as of April 3, 2020 (<https://www.worldometers.info/coronavirus/>). The containment of COVID-19 and the management of patients is the need of the hour. To tackle this medical emergency, numerous scientists are extensively working on the characterization of SARS-CoV-2 for accurate diagnosis and designing the appropriate vaccines and therapies to cure COVID-19 patients. In addition, various organizations are also actively involved in generating the vital statistics and information about the COVID-19 outbreak. This generates plenty of data or information in the form of widely spread literature, resources, videos, etc. One of the major challenges is to manage/accumulate this information at a single platform in a user-friendly manner, to make it approachable to the wider audience such as the scientific community, clinicians, etc. for the containment of COVID-19 patients. Since, the delay in diagnosis and the lack of effective drugs and vaccines for COVID-19 results in increasing the mortality rate day by day (69). There is a need to accelerate the research in the development of adequate vaccines and drugs. Hence, the present study is an attempt to compile this widespread information associated with SARS-CoV-2 or COVID-19 at a single user-friendly web-based

platform named “CoronaVIR” (<https://webs.iiitd.edu.in/raghava/coronavir/>), along with predicted novel potential diagnostic, vaccine and drug candidates based on literature and bioinformatics analysis.

In the CoronaVIR, we have integrated mainly four modules which include “Genomics”, “Diagnosis”, “Immunotherapy”, and “Drug Designing”. The “Genomics” module provides 53 whole-genome sequences from various countries and sequences of 10 proteins, etc. This will facilitate the users/researchers for the genomic-analysis of SARS-CoV-2 to scrutinize vital information of structural and functional components, eventually to design vaccine, drug molecules. The “Diagnosis” module provides detailed information regarding currently-in-use diagnostic tests. Additionally, we have predicted novel five universal primers candidate sets for the diagnosis of COVID-19 based on 53 genomic sequences of SARS-CoV-2 strains of different parts of the globe. These diagnostic primers need experimental validation as they are designed by Insilco analysis only. Further, the “Immunotherapy” module of CoronaVIR maintains various peptide and RNA-based immunotherapeutic candidates for COVID-19. In the current study, we have proposed 17 potential vaccine candidates that can activate the immune system based on our bioinformatics analysis. Importantly, five peptide sequences, i.e. LQLPQGTTLPKGFYA, VILLNKHIDAYKTFPTEPKKDKKKK, EITVATSRTL, GKGQQQQGQTV, and SELVIGAVILR are predicted by most of the immuno-informatics tool such as LBtope, CTLPred, VaxinPAD, ProPred, and Propred 1 and also reported in IEDB. This analysis indicates that these epitopes have potential of B-cell, T-cell activation with MHC-binding and vaccine adjuvant capability; eventually can activate almost all the arms of our immune system. Furthermore, these five vaccine candidates are also mapped on six SARS-COV-2 strains from different parts of globe. This reveals their utility on universal aspects. Besides peptide-based vaccine candidates, we have also discovered siRNA-based therapeutics and nucleotide-based vaccine adjuvants for COVID-19 using insilico approach. Eventually, experimental researchers can further explore these potential vaccine candidates to confirm their clinical utility. Apart from that, Drugs are the key means to combat this global disaster of COVID-19. Hence, the “Drug Designing” module is integrated to manage information of nine potential drug targets, their structures, number of drug molecules, drug delivery peptide-based vehicles (CPP). Recently, Wang et al. has shown in their study that a human monoclonal antibody 47D11 binds to SARS-CoV-2 and SARS-CoV, and potently inhibits the virus’ infection of Vero cells (70), which suggests that monoclonal antibodies can

act as therapeutics to treat COVID-19 patients. Although, clinical validation is still needed to confirm their potential application in combating COVID-19.

Taken together, CoronaVIR is a comprehensive web-based platform, which accommodates widely scattered information of different aspects, i.e. genomics, diagnosis, therapeutics of the SARS-CoV-2 in a user-friendly manner. We anticipate this would facilitate the researchers involved in managing the COVID-19. Moreover, the novel suggested potential diagnostic, vaccine and therapeutic candidates based on insilico analysis might further help in designing effective diagnostic tools and vaccines for COVID-19, and hence eventually help in combating this COVID-19 medical disaster.

Competing interests

The authors declare no competing financial and non-financial interests.

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Authors Contributions

S.P., D.K., H.K., N.S., A.D., S.S. collected the data and processed the datasets. S.P., H.K., D.K., N.S., A.D., S.S., P.A., C.A., and L.M. analyzed and predicted candidates. D.K. and H.K., developed Genomics module. H.K. and L.A., developed Diagnosis module. S.P., N.S., A.D., and D.K. developed Immunotherapy module. S.P., S.S., and P.A. designated Drug Designing module. S.P., D.K., H.K., A.D., P.A., C.A., and G.P.S.R created the back-end server and front-end user interface. S.P., H.K., D.K., N.S., A.D., P.A., L.M., and G.P.S.R. analyzed the results. S.P. H.K., D.K., C.A., N.S., and G.P.S.R penned the manuscript.

G.P.S.R. conceived and coordinated the project, facilitated in the interpretation and data analysis and gave overall supervision to the project. All authors have read and approved the final manuscript.

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Supplementary Material

A web-based platform on COVID-19 to maintain Predicted Diagnostic, Drug and Vaccine candidates

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731 Table S1: List of 53 Genome sequences that are maintained in CoronaVIR that are used for
732 designing the “Universal” primers for the diagnosis of COVID-19 (SARS-CoV-2).

Accession ID	Source country	Length (No of nucleotides)	Strain
MT012098	India	29854	SARS-CoV-2/29/human/2020/IND
MT050493	India	29851	SARS-CoV-2/166/human/2020/IND
MT152824	USA	29878	SARS-CoV-2/WA2/human/2020/USA
MT135042	China	29903	SARS-CoV-2/231/human/2020/CHN
MT135041	China	29903	SARS-CoV-2/105/human/2020/CHN
MT135043	China	29903	SARS-CoV-2/233/human/2020/CHN
MT135044	China	29903	SARS-CoV-2/235/human/2020/CHN
MT126808	Brazil	29876	SARS-CoV-2/SP02/human/2020/BRA
MT123290	China	29891	SARS-CoV-2/IQTC01/human/2020/CHN
MT123291	China	29882	SARS-CoV-2/IQTC02/human/2020/CHN
MT118835	USA	29882	2019-nCoV/USA-CA9/2020
MT106054	USA	29882	2019-nCoV/USA-TX1/2020
MT106052	USA	29882	2019-nCoV/USA-CA7/2020
MT106053	USA	29882	2019-nCoV/USA-CA8/2020
MT093631	China	29886	SARS-CoV-2/WH-09/human/2020/CHN
MT093571	Sweden	29886	SARS-CoV-2/01/human/2020/SWE
MT072688	Nepal	29811	SARS0CoV-2/61-TW/human/2020/ NPL
MT066175	Taiwan	29870	SARS-CoV-2/NTU01/2020/TWN
MT066176	Taiwan	29870	SARS-CoV-2/NTU02/2020/TWN
MT049951	China	29903	SARS-CoV-2/Yunnan-01/human/2020/CHN
MT044258	USA	29858	2019-nCoV/USA-CA6/2020
MT044257	USA	29882	2019-nCoV/USA-IL2/2020
MT039890	South Korea	29903	SNU01
MT039887	USA	29879	2019-nCoV/USA-WI1/2020
MT039873	China	29833	HZ-1
MT039888	USA	29882	2019-nCoV/USA-MA1/2020
MT027063	USA	29882	2019-nCoV/USA-CA4/2020
MT027064	USA	29882	2019-nCoV/USA-CA5/2020
MT027062	USA	29882	2019-nCoV/USA-CA3/2020
MT019529	China	29899	BetaCoV/Wuhan/IPBCAMS-WH-01/2019
MT019531	China	29899	BetaCoV/Wuhan/IPBCAMS-WH-03/2019
MT019533	China	29883	BetaCoV/Wuhan/IPBCAMS-WH-05/2020
MT020881	USA	29882	2019-nCoV/USA-WA1-F6/2020

MT019532	China	29890	BetaCoV/Wuhan/IPBCAMS-WH-04/2019
MT020880	USA	29882	2019-nCoV/USA-WA1-A12/2020
MT019530	China	29889	BetaCoV/Wuhan/IPBCAMS-WH-02/2019
MT007544	Australia	29893	Australia/VIC01/2020
MN996528	China	29891	WIV04
MN996530	China	29854	WIV06
MN996527	China	29825	WIV02
MN996531	China	29857	WIV07
MN996529	China	29852	WIV05
MN988669	China	29881	2019-nCoV WHU02
MN994468	USA	29883	2019-nCoV/USA-CA2/2020
MN988668	China	29881	2019-nCoV WHU01
MN997409	USA	29882	2019-nCoV/USA-AZ1/2020
MN994467	USA	29882	2019-nCoV/USA-CA1/2020
MN988713	USA	29882	2019-nCoV/USA-IL1/2020
MN938384	China	29838	2019-nCoV_HKU-SZ-002a_2020
MN975262	China	29838	2019-nCoV_HKU-SZ-005b_2020
MN985325	USA	29882	2019-nCoV/USA-WA1/2020
MN908947	China	29903	Wuhan-Hu-1
NC_045512	China	29903	Wuhan seafoodWuhan-Hu-1

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736 **Table S2: No of the nucleotide-based vaccine adjuvants and siRNA-based vaccine**
737 **candidates for each of available proteins of SARS-COV-2 (Accession ID MN908947)**
738 **designed using “VaccineDA” and “desiRM” for vaccine adjuvants and siRNA,**
739 **respectively.**

Protein name	No of Vaccine Adjuvants	No of siRNA candidates
Envelope protein	200	25
Membrane glycoprotein	642	45
Nucleocapsid protein	1230	35
Orf3a	800	75
Orf1ab	5251	2162
Orf6	156	168

Orf10	89	3
Surface protein	3794	699
Orf7a	340	2
Orf8	338	12

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