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Devising a Multi Epitope Vaccine towards the Dengue Virus using the Computational Method in Asian Region

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ABSTRACT

Dengue is one of the major mosquito-borne diseases that still threaten humans and kill countless people. It is caused by a positive-stranded RNA virus that included the family of Flaviviridae. Dengue fever is an exquisite feverish viral disease dispatched by Aedes mosquitoes' sting, posing any one of the four dengue viral serotypes. This virus transmits through a vertical transmission way using a full unique system. Unfortunately, there is no still effective developed vaccine to eradicate this disease. Computational methods were used in this work to build and we suggest a multi-epitope vaccination for the dengue virus in Asia. Epitope conservation was taken into account because Dengue virus is an RNA virus, and all selected epitopes were 100% conserved. Antigenicity of the final multi-epitope vaccine component was 0.7055. Disulfide engineering was conducted at an area of high mobility to improve vaccine protein stability. In addition, codon adaptation and in silico cloning was used to guarantee that the planned subunit vaccine in E. coli *was expressed at a greater level. Lastly, a molecular docking and simulation analysis was carried out for the vaccination protein and the TLR-4 receptor in order to assess the binding free energy and stability of the combination for this reason, the suggested in silico vaccine has to be tested for safety and immunogenicity in order to guarantee an active immunity against the Dengue virus.*

Keywords: Dengue, Immunoinformatics, Vaccine, Epitope, Microbiology

Abbreviations: SAAY: Ala-Ala-Tyr; CTL and HTL epitopes: Combined epitope; CTL: Cytotoxic T-lymphocyte; E. coli: Escherichia coli; GPGPG: Gly-Pro-Gly-Pro-Gly; HTL: Helper T- lymphocyte; I-TASSER: Iterative Threading Assembly Refinement; JCAT: Java Codon Adaptation Tool; KK: Lys-Lys; LBL: Linear B-Lymphocyte; MD: Molecular Dynamic; MHC-I: Major Histocompatibility Complex-I; MHC-II: Major Histocompatibility Complex-II; Rg: Radius of Gyration; RMSD: Root-Mean-Square Deviation; RMSF: Root Mean Square Fluctuation; SOPMA: Self-Optimized Prediction Method with Alignment; TLR4: Toll-Like Receptor 4; WHO: World Health Organization; SRA: Sajidur Rahman Akash; MIH: Md. Imran Hossain MSA: Md. Sarafat Ali

INTRODUCTION

Dengue is a serious mosquito-borne disease that carries pestilence ability. An arbovirus is known as Dengue virus and that's an etiological agent. It's a serious known health warning for numerous emerging tropic lands. They had been established in all respects of tropical territories of the world over 60 years [1]. In different tropical territories, southeastern Asia is obtained as the area with a rich outbreak of this affliction. The Amazing hemorrhagic model

of dengue disease has become the main dangerous cause of death for the local bodies of southeast Asia. Francisco Pinheiro, a former Empiric of the Division of Disease Prevention and Control, and the Special Program for Vaccines and Immunization, Pan American Health Organization (DC, USA), told that maximum discharge of dengue could be marked in southeast Asia, specifically in Vietnam and Thailand, those simultaneously account for more than two-thirds of the total reported occurrences in Asia [2]. This infection has also been reported in non-tropical territories in Asia for example East Asia and China [3]. Dengue takes place sporadically in Bangladesh at a broad pestilence in 2000 initiated the virus until 1964. At that time, we found Dengue from the time it was first denoted in Bangladesh and recognized factors are beneficial to future dengue hemorrhagic fever pestilences [4]. The time of the epidemic was probably due to the induction of a dengue virus strain from a close endemic country, probably Thailand. Resignation of dichlorodiphenyltrichloroethane (DDT) spraying, climatic, socio-demographic, and lifestyle generators also contributed to pestilence transmission [5]. Even though it increased in alternate years, a maximum number of cases was proclaimed in 2002. In this way, we decrease the notification numbers which may be an artifact of the surveillance system [6]. Poll-based-serological observation gives a hint that dengue transmission runs to be usual. Without intelligent interventions, unplanned urbanization, environmental downfall, rising population motility, and financial factors will take up dengue risk in the future. That's why it's an urgent need to develop a vaccine for these major risky areas. In this research, we are required to design a vaccine using immunoinformatics approaches against the dengue virus that is linked to the Asian region especially for the Asian region.

MATERIALS AND METHODS

Proteome salvation and antigen extracts

We select probable HCMV proteomes from the viprbrc website database to pop out antigen choice [7]. Spike proteins are set on the surface membrane of the HCMV. They collaborate with this protein in order to link up with the human host and enter their genome [8]. With the exact link of glycoproteins in creating disease, we measured the spike protein of the HCMV for the multi-epitope vaccine plan. In this process, we first selected the dengue virus's protein sequence, which had been downloaded in a fasta file. Then the collected antigens are investigated by the ddg-pharmfac website database with an optimum threshold value of 0.4 was set for it [9]. Finally, we selected the spike protein which had the most powerful antigenic score for additional investigations.

Forecast and evaluation of helper T-lymphocyte epitopes

Helper T-cells (HTLs) are an important part of adaptive resistance that sees different antigens and begins B and cytotoxic T-cells ending within the loss of the damaging pathogen. to find out the HTL epitopes, we did the IEDB's MHC class II necessary allele forecast tool. The HTL epitopes were chosen to support a percentile level of fifty doing the Agreement method [8] These epitopes were more tested and supported antigenicity using vaxijen server v2.0 [10].

Forecast and evaluation of cytotoxic T-lymphocyte epitopes

Cytotoxic T lymphocytes have the ability to kill phagocytes by directly this process [11]. For this reason, we use the NetCTL v1.2 server. The collected epitopes were again tested with Vaxijen v2.0, Toxiprod and Allerrtop v2.0 servers. All parameters kept default for all the foretells[10-13].

Forecast and evaluation of linear B Lymphocyte Epitopes

To secure humoral or antibody medication safely B cell epitopes are needed [14]. For which, an online portal named iBCE-EL we took the help of this with default levels [15].

Modelling of multi-epitope vaccine

The vaccine was created using the chosen CTL epitope, HTL epitope, and LBL epitopes as well as a complete adjuvant that was followed by the relevant linkers [14-16]. Here, for recognition by viral glycoproteins, we used TLR4 agonist as an adjuvant [17,18]. Therefore, 50S ribosomal protein (NCBI ID: P9WHE3) was appreciated as the adjuvant to improve the immunogenicity of the vaccine candidate. The adjuvant was associated with linker EAAAK. In contrast, the selected CTL was combined with (AAY) linkers, the HTL was associated with (GPGPG) linkers and the LBL was connected with (KK) linker [14-16].The AAY linker was used to influence protein balance. [19,20].

Physicochemical and immunological evaluation

The vaccine's functional characteristics were forecasted by applying the ProtParam database [21]. Again, by

cooperation of Vaxijen v2.0[22] MHC-1 immunogenicity(12)(10) Allertop ; Biosoland, SOLpro website we evaluated the immunological attributes of the vaccine [9].

Secondary construction forecast

When we gave the vaccine model to the SOPMA server and PSIPRED v4.0 server, it identified the construct's two-dimensional basic peculiarities such as alpha-helix and random coils [23].

Homology modelling, 3D construction clarification and validation

To build the structure prognosis, we delivered the created vaccine into Galaxy web an online portal [24]. Then we refine the vaccine from the galaxy web to breed vaccine composition [25]. From the portal the accomplish building was downloaded and then according to the highest RMSD rate and effectiveness number of the quietest the selected structure was named. Using the PyMOL v2.3.4 software we saw the elegant and distinguished formation which was envisionly practiced. The ProSA-web accessory and Procheck proved the Ramachandran plot and z-point momentous [26].

Molecular docking investigations

It reveals the essential contacts between modeled protein and receptor units. For this instance, we gave up the accomplished vaccine model as ligand and TLR4 protein as a receptor molecule into the ClusPro v2.0 site, for docking study[27]. We chose the TLR4 receptor (PDB ID: 3W3M) and took it from the PDB site.

Dynamics simulation study

For the purpose of molecular dynamic simulation, we used an instrument that was server-based. By that, we could critically estimate the dynamics and security of the vaccine-receptor fear. The illusion was removed from the iMODS site[28].

Protected rejoinder simulation

The proper build was relinquished on the C-IMMSIM v10.1 site and the created responses were restored for proper judgment, to evaluate the expedite secure response of the vaccine [29]. As reported, we agreed on the tiniest interlude point of 30 days between two applications [30].

Codon adaptation and in silico cloning Technique

Codon optimization is more needed according to the special organism as the appearance of an alien gene in an organism is concerning. Depending on the codon change the construct was relinquished on the JCat server. Based on the codon adaptation ratio (CAI) preference and guanine-cytosine content, the modified course was evaluated. The body in silico cloning plan was accomplished in Snap Gene v4.2.

RESULTS

Best antigenic protein selection

From the value on the basis of antigenicity the design protein scored with an antigenic point of 0.7055 (Vaxijen).

Possible CTL epitopes

To bind up the main vaccine we took the top five vaccines from numerous Epitopes on the basis of antigenicity value.

Possible HTL epitopes

There above, almost numerous HTL epitops were selected by each one for originally practicing the IEDM site. Top five values of HTL epitopes could join better than from the rest onces.

Possible LBL epitopes

We took two antigenic epitopes among all direct B cell epitopes whose are non-allergenic negative Grand average of hydropathicity

Vaccine construct and fundamental premises

We formulated the vaccine by the (5 HTL, 5 CTL, 1 LBL) on the basis of antigenicity and toxicity. Among the 178 Amino acids long the vaccine finally formed.

Tertiary structure, sophistication and evaluation

In this section we took the highest five models by using Galaxy Web. We selected the model which had the minimum C-value that was suggested by the site. Refining the model that we formed the vaccine showed that in Ramachandran graph it surpluses 93.8% in the considerable region, with a GDT- score, RMSD, MolProbity 2.047, 1.276 Clash 1.3 also rotamers score 0.0. Finally by the Procheck online site and additional file with all findings and ProSA-web server the Z score average for the vaccine is -8.81 (Figure 1).

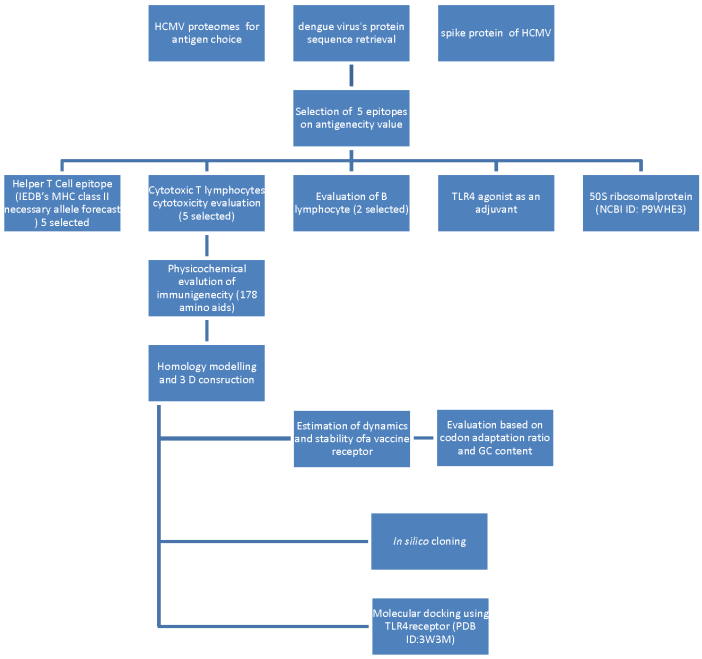

Figure 1: Immunoinformatic designing of multi epitope vaccine against dengue virus.

Molecular docking incestigation

Putting the Clus Pro v2.0 server it should 30 docked models with the different positions where we selected the least energy value with the additional file. Therefore, we put model 2 in the dangling role with an energy score of -1401.2.

Molecular dynamics simulation experiment

In this experiment we used iMODS site and the NMA evaluations were submitted to the internal complex, whether the average life B- factor map, Eigenvalues, Variance, Covariance map, Elastic network are displayed on 10 (A), 10 (B), 10 (C), 10 (D), 10 (F), 10 (G).

Exempt rejoinder simulation

Special pathogens expressed produced actual immunological aspects which are confirmed in 11A to 11G. Antigen and immunoglobulin value showed 11A, B lymphocytes cell; which are IgM and IgG in 11B, plasma B lymphocytes count as sub-divided per isotope (IgM, IgG1, IgG2) IN 11C. The other value showed in 11C to 11G.

Codon evolution and in silico cloning

To develop their key-factor according to the *E.Coli* by the JCat site we optimized the codons in the vaccine which was created. Lastly, the formed size of the vaccine cloning product is 5907 bp and the vector was 5369 also insert 546 bp (nucleotide base pair).

DISCUSSION

The treatment of dengue should take as far as possible from the concept of going obviate the pathogen and restricting the perplexity [31]. Generally, the practice of supportive and evidential methods is broadly used for dengue treatment. Dispensation of fluid treatment has grown also in dengue administration and that's practically based on the austerity

of infection [32]. During regular strain of dengue, oral liquid replacement is enough and there's no necessity for hospitalization. But with difficult occurrences of dengue contamination, liquid replacement should be cautiously applied and must be made under close inspection during a sanitarium [33]. Enteral liquid displacing by both colloids or crystalloids should be considered to prevent dengue illness [34]. Primary follow-up of laboratory tests might be practised to assess the hematocrit and platelet calculation; it's thought that a progressive increase in hematocrit has a great opportunity of manufacturing damage [35]. That's why to prevent this dengue disease from the human body it's urgent to develop a vaccine[36-40]. At times the strength of mosquito control in Bangladesh are larvicides, adulticides, extra fogs, mosquito coils, and aerosol splashes, etc. During the 2012-2013 financial years Dhaka city corporation budget 6% of the expenditure was assigned to mosquito restriction. But yet this is not an effective approach to stop this pandemic. For this reason, the vaccine is the only solution for it. Various types of candidates are already available in the research field but there's have no established one yet. If in lab follow this instruction of our designed vaccine, hope that the dengue viral disease problem will be solved as we maintained the highest level of safety tools and methods [41-47].

CONCLUSION

Although the initiation of a Thai strain was the likely reason of the 2000 pandemic, a mix of socio-demographic and climatic constituents inflamed and sustained endemic transmission afterward. In 2002 since the most important epidemic was described but no serious additional control measures having been initiated, in contrast to Indonesia, Thailand, Sri Lanka, over al Asian countries. That's why it's an urgent task to develop a vaccine to prevent this epidemic in risky regions. We hope our predicted vaccine will be the best suited vaccine for dengue virus infection.

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CONFLICT OF INTEREST

The author declares no conflict of interest on this paper.

AUTHOR CONTRIBUTIONS

SRA, MIH designed the project and performed the experiments; MSA evaluated and interpreted the data; SRA, MIH prepared the draft manuscript; SRA, MIH, MSA finalized the manuscript. All authors approved the final version of the manuscript.

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