Viral Immunoinformatics: A Potential Technological Armamentarium Against Dengue Virus

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Introduction

Dengue is a mosquito borne tropical fever caused by Dengue virus (DENV) a single positive-stranded RNA virus of the family Flaviviridae. DENV is transmitted to humans via Aedes mosquito (principally *A. aegypti*). Annually it is estimated that dengue causes threat to more than 2.5 billion human population in over 100 countries [1]. To exacerbate the present situation, there is no sustainable preventive measure (especially any registered drug) against dengue. As per the reports from Reuters and CNN, for the first time in 2016 Dengvaxia, a moderately effective vaccine became commercially available in 11 countries namely Mexico, the Philippines, Indonesia, Brazil, El Salvadorm Costa Rica, Paraguay, Guatamala, Peru, Thailand, and Singapore [2-4] yet an absolute remedial measure or a licensed vaccine is still elusive worldwide [5].

The mounting prevalence of new viral diseases and recurrent viral epidemics have agitated therapeutic and preventive measures. The high rate of mutations of viral genes further puts supplementary pressure on the existing developmental efforts. The procedure of drug discovery from the bench to the market is an extensive and costly process. Further it has been accounted that development of an effective licensed drug takes more than 10 years and costs some two billion dollars [6]. The universal cost of dengue cases is determined to be US$9 billion [7]. Since the viral epidemics keep on changing every one or two year, drug development would not be feasible for new viruses. Drugs serve as curatives; while vaccines serve as an as attractive alternative preventive means, since their development costs are comparatively lower.

In the dearth of time and expense to overcome dengue by absolute wet lab methodologies, Virus immunoinformatics that basically comprises structure based drug designing (SBDD) for viral diseases, provide new opportunities to design drugs and vaccines against dengue. SBDD usually employs use of computational approaches such as molecular modelling, docking, molecular dynamic simulations, virtual screening, de novo design of new ligands, optimization of known ligands by evaluating proposed analogs within the binding cavity. Some of the structure based drug designing approaches undertaken in case of dengue virus are mentioned underneath.

Structure based drug designing in DENV

Four discrete serological types of dengue virus (DENV) have been identified namely, DEN1, DEN2, DEN3 and DEN4. All the serological types have the three structural component in common that form major constituent of the virus v.i.z capsid, premembrane (prM) and envelope (E) protein. Among all the three components the envelop protein is responsible for instigation of the fever since it mediates entry of the virus by interacting with host cell surface receptors. Hence envelop protein is crucial as potential target for the development of antiviral agents and serves important for vaccine development [8]. The structure of the E protein (PDB code: 1OKE) reveals presence of a hydrophobic pocket occupied by the detergent n-octyl-β-d-glucoside (β-OG). The β-OG binding site is proposed to be an apt target for de-

veloping small-molecule inhibitors involved in virus-host membrane fusion process. Computational approaches involving docking-based virtual screening have identified 23 small molecules that likely bind to the β-OG binding site. Among the identified compounds, one of the compound surpassed as an effectual inhibitor with EC50 = 3.1 μM and depicted noticeable antiviral activity with a good therapeutic index. In order to get atomised details of the interaction between the inhibitor and protein E molecular dynamics simulations were performed, thus opening avenues for future ligand optimization endeavours. Such in-silico studies have highlight the likelihood of using a new class of DENV inhibitors against dengue and have caused a major leap in dengue research [9].

The NS2B-NS3 protease complex is indispensable for the dengue virus replication process. The complex is a proficient target for antiviral discovery because a drug could inhibit the viral polyprotein processing. Furthermore, the protease complex is highly conserved among all the four DENV serotypes, thus it serves as a plausible target that a drug would be evenly effective against all of them. Computational approaches employing computational alanine scanning mutagenesis, sequence, structure conservation, and other structure-based characteristics were used to identify influential residues on the function of the Dengue NS2b- NS3 Protease [10].

Conclusion

The present era of blooming research in bioinformatics, proteomics, immunogenomics, structural biology and other sciences have stimulated the augmentation of drug designing where the computer assisted approaches serve to identify appropriate drug targets for eventual development of drugs. Computer-assisted drug and vaccine discovery is a relatively new field, which are yet to be explored. Another very new emerging concept is development of peptide vaccines. Peptide vaccine formulation have an edge to the normal vaccines in terms of their speed and cost of development. The recurrent incidences of dengue epidemics, make rational design of peptide vaccines an important alternative to combat against the disease. In this endeavour, computer-assisted approaches provide promising drug and vaccine identification strategies. Though the wet-lab experimentations are obligatory to demonstrate the viability of these relatively newer approaches yet the computational approaches reduce the time and cost of drug designing procedures tremendously.

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