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The development of novel HPV Drugs by HDAC inhibitor based upon applied bioinformatics tool and their specialized algorithm

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ABSTRACT

The HPV infection, which is the sole cause of cervical cancer, is a malicious threat for developing countries, for instance, Indonesia. Drug for coping HPV infection have been sold in the market namely SAHA or Vorinostat. Mainly, it works by inhibiting the Human Deacetylase Enzyme (HDAC) class II *Homo sapiens*. However, due to the contradicting report on its efficacy, a novel drug should be developed to remedy the resistance problem. Some groups have successfully developed novel HDAC inhibitors, based upon computational drug design.

Keywords: *HPV; SAHA; bioinformatics.*

1. INTRODUCTION

Cervical cancer is becoming a menacing threat in developing countries, and it is progressing at an alarming rate [1,69,73,74,71,72]. As the causal relation between Cervical cancer and Human Papillomavirus (HPV) was correctly determined by Harald Zur Hausen, the medication for this malicious disease could possibly be developed [2,3]. HPV is a non-enveloped, icosahedral capsid, ~7.9 kb in length and 55 nm in diameter, circular double-stranded DNA virus that belongs to the Papillomaviridae family [4,5]. Over 120 different genotypes have been identified. HPV genotypes can be divided into low and high-risk categories based on the spectrum of lesions they induce [6]. HPV 16 and HPV 18 are the two most frequently detected HPV types in squamous cell carcinomas of the cervix [7,66]. HPV is responsible for encoding the E7 oncoprotein, which would eventually be coopting the expression of Histone Deacetylase (HDAC) Enzymes [8,9]. This disruption is one of the primary causes of the uncontrolled proliferation of cancer growth [10].

Today, curative measures to combat cervical cancer have been sold in the market. SAHA, or Vorinostat, is one of the most important drug for coping with Cervical cancer [11,12]. It was proven that the HDAC could be inhibited successfully by SAHA [13,14]. However, the efficacy of SAHA is disputable, as there are complains about its side effects [15,16]. In clinical use, SAHA had poor pharmacokinetic properties and adverse effects [17,18]. Thus, the modification of SAHA could be a feasible alternative in Cervical cancer drug development [19,65,68].

2. IN SILICO HPV DRUG DEVELOPMENT

Asia Pacific region is an emerging area of rational drug development, especially for synthetic and herbal lead compounds [20]. Available drug inhibitors for HIV; arthritis; and antitumor drug, were successfully designed by using modern bioinformatics tools [21,14]. In line with those studies, we tried to develop a computational pipeline for developing HPV drugs [25].

The computational time and space complexity of HPV rational drug design has been proved to be efficient [26]. Thus, the methodology of our research always comprises of different, albeit, coherent parts, namely multiple sequence alignment; Ligand preparation; Molecular Docking; and Molecular Dynamics [25]. In this end, our computational procedures could eventually yield results that could be further developed as drug candidates.

Our very first study on HPV drug candidates is the computational study on SAHA and TSA [12]. We concluded that SAHA is the best ligand as a template for new drug candidates. However, as SAHA has certain side effects, we try to mitigate them by modifying its structure [16]. Hence, we have successfully generated SAHA derivatives and tested them by molecular docking and dynamics tools [27,28]. Hence, we elucidated the molecular interactions of the ligands in high-resolution graphics, as shown in figures 1 [29]. We also used boron in the modifications of SAHA, Ligand Nova2 (513246-99-6) obtained as the best result of docking[30].

2.1. Special Algorithm for HPV Drug Development.

However, the proteomic based approach is not the only methods that are available in the market. The short interfering (si)RNA has been successfully silencing the oncogenic E6 and E7 genes in HPV and could be possibly developed as drug candidates as well [31-33]. Moreover, the transcriptomics pattern of the HPV-infected cells could pave the way for a more effective medication [34,35]. Micro (mi)RNA, as one of the transcriptomics pattern, could act as a specific marker for cervical cancer [36]. Besides transcriptomics approach, epigenetics also play a role in providing a specific marker for the malignancy of cervical cancer, especially by providing the DNA methylation patterns [37]. Last but not least, Valproic acid could be utilized as epigenetics based drugs against cervical cancer [38].

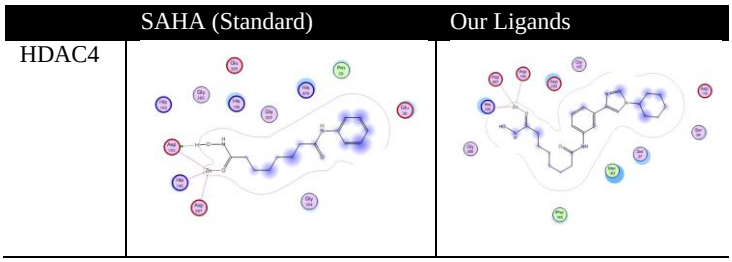

Figure 1. The molecular interaction of HDAC4-SAHA and HDAC4-our ligand [29].

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The utilization of sophisticated HPV bioinformatics tools could only come true by using specialized algorithms. In this end, several algorithms are developed for that purpose. One of the simplest, hence is very useful, is Grid Box Determination [39]. This algorithm is quite handy for determining the 3D space for the docking environment [40,41]. The focal point of the modeling is providing the Cartesian coordinate of atomic coordinate in a 3D manner, and within the three-axis (X, Y, Z). It should be noted that Grid Box Determination is the most essential requirement to start the docking method [42].

The sophistication of a rational drug development begins where more complex algorithm could apply. Enter Nosé-Poincare-Anderson (NPA), is originally a combination of three different computational methods [43]. Nosé applies Hamiltonian as trajectories propagation towards the canonical ensemble, in order to fine-tune the properties, while the Poincaré time-transformation is another Hamiltonian system for time-transformation. We can construct a Hamiltonian system using a Poincare time-transformation and show that it can generate trajectories in the canonical ensemble (N, V, T constant).

Meanwhile, the molecular docking of drug-receptors should be fitted with a feasible method. The Lamarck Genetic Algorithm (LGA) has been developed for molecular docking, where the calculation of the involved charged and energies between the ligand and receptor could be conducted easily [39]. The principle of LGA involves modeling the incorporation of phenotype into its genotype for passing it to the next generation [44]. The phenotype is the representation of the ligand, while the genotype is its chromosome [45].

Molecular mechanics force fields (MMFF94x) is the focal feature of computational dynamics for rational drug design [46]. Although it was mainly designed for small organic compounds, MMFF94x has proved itself to be reliable for ligand-receptor interaction study [47]. There are several parameters that can be considered for MMF94x methods, namely molecular geometries; conformational and stereoisomeric energies; torsional barriers and torsion-deformation energies; intermolecular-interaction energies; intermolecular-interaction geometries; vibrational frequencies; and heats of formation [46]. Those parameters have been included in the MMFF94x methods in molecular dynamics packages that we use, such as MOE and GROMACS.

Molecular simulations, especially the one that involves protein modeling, always include several important parameters that derive from their physicochemical properties. They are, namely, van der walls; electrostatic interaction; Hydrogen bonds; and hotspot interface [48]. Interaction computational model for protein docking is assumed as applies rigid body for simplifying the need for time complexity [49].

2.2. The Possibility for Benchmarking Available Tools.

Traditionally, disease targets identified through a long and complicated process. The advances in homology modeling have provided fast and efficiently, despite being less accurate means to identify the target [50], in silico techniques will facilitate the identification process[51].

Benchmarking bioinformatics tools are considered as a standard practice in ensuring consistency in bio-computation pipelines [52]. The most common benchmarking theme is definitely the multiple sequence alignment methods, whether for protein, DNA, or RNA [53,54]. However, as more sophisticated computational methods were developed for bioinformatics research, complex methods such as homology modeling, molecular docking and dynamics are started to be benchmarked as well [55-57].

The different tools are not directly comparable. They need to be calibrated with a standard. For example, the benchmark of Autodock versus MOE needs to be calibrated with a standard or dataset. In this respect, for developing HPV drugs, SAHA or its derivatives could be utilized as fine-tune standards for benchmarking purposes [58].

3. FUTURE SCOPE

The review paper represents a scientific review of the modification of SAHA by use bioinformatics tools as an alternative in cervical cancer drug development. Systems biology approaches have the potential to transform drug discovery and development. Large-scale gene, protein and metabolite measurements ('omics') accelerating the generation of hypotheses and testing in disease models. Computer simulations integrate knowledge organ and system response levels to help prioritize targets and the design of clinical trials [59,70]. By knowing the biological systems from HPV, can be attributed to use nanotechnology in drug development. Nanotechnology has been studied extensively for improving the management of cervical cancer and are used for the diagnosis of HPV to increase its sensitivity [60]. One application of nanotechnology is biosensors that can be used to detect cervical cancer in the early stages of the disease [61]. Not only that, nanotechnology can be used as an effective strategy for protein delivery [62].

Large scale genome and protein annotation project will be useful for developing drug [63]. Proteomics strategy can be used to analyze HPV-transformed cells in cervical cancer. In viral infections, neutralizing antibodies are very efficient for blocking the circulation of virus particles, but not active in the cell-bound to the virus. To find a vaccine or drug that is appropriate, it is essential to identify immunogenic epitopes in early infection and which are not presented displayed on the host proteome. [64,67]

4. CONCLUSIONS

With the threat of cervical cancer in many countries, the development of treatments should be considered. We believe that further studies in SAHA and some alternative treatments should be done in the near future, and we believe that the utilization of bioinformatics tools is an important method that can be utilized in further studies. Modifications of existing drugs like SAHA and or a completely novel new drug can be developed using the tools and algorithms readily available to use.

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