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Editorial

Impact of Virtual Screening on HIV Reverse Transcriptase Inhibitor Discovery

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Introduction

Human immunodeficiency virus (HIV) has become one of the most dangerous viruses after 30 year's spread in the world. The highly active antiviral therapy (HAART) is effective in suppressing the virus, but it is impossible to cure the infection thoroughly. As the only treatment in clinic, HAART has saved millions of lives from AIDS and related diseases. HAART depends on combination of several antiviral drugs against different targets of HIV life cycle [1]. These targets are usually important enzymes or proteins of HIV, including reverse transcriptase (RT), protease (PR), integrase (IN), gp120 and gp41, etc. [2]. The infection is a complex interaction between HIV and human. Numerous host proteins are involved in the infection process. These host proteins, such as receptor and co-receptors, are also effective targets for anti-HIV research [3,4]. Among all the effective targets, RT is the first one to be targeted for HAART. There are 19 RT inhibitors have been approved by FDA for the treatment of AIDS. Although more than 30 drugs are currently used for clinical treatment of AIDS, drug resistant viruses have emerged against each drug [5]. This prompts scientists to make their efforts for novel drug discovery.

Virtual screening (VS) is a drug discovery technology based on the development of computer science. With the great improvement of calculation speed and accuracy, VS has become one key factor in modern drug discovery. There are two kinds of VS: the structure based VS and the ligand based VS [6]. In this paper, we put our emphasis on structure based VS. The structure based VS is a powerful tool when a reliable crystal structure of the target protein is available. There are more than 300 HIV RT crystal structures are available in the Protein Data Bank (PDB). This is a vast source for RT inhibitors discovery through VS. Database of drug candidates is another important factor for successful VS. There are many commercial or scholarly free databases are available, including ZINC (www.zinc.docking.org), SPECS (http://www.specs.net) and ChemBridge (http://www.chembridge.com), etc. Millions of compounds from these databases are provided for structure based VS. Moreover, the number of compounds is increasing with millions every year. How to find an effective HIV RT inhibitor form the huge number of compounds? VS are the choice. An excellent program is very important for successful VS. Many programs have been developed for VS. Auto Dock is the representative of free VS tools. Auto Dock is designed by the Scripps Research Institute and widely used in drug discovery. Besides Auto Dock, DOCK, GOLD and MOE are also popular programs for VS [7-9].

A substantial number of studies have been conducted to discover potential HIV RT inhibitors through VS [10-12]. Here are just some examples. Ten compounds with HIV RT inhibitory activity were discovered from Indonesian Herbal Database through VS using Auto Dock4 [13]. Two compounds which inhibit the activity of RT and block HIV replication were discovered from a library containing 2864 National Cancer Institute (NCI) compounds via VS [12]. In another study, three compounds with low-micro molar antiviral activity against both wild type and Y181C HIV-1 strains were selected from more than 2 million compounds via VS using three RT structures. Two structures are wild type with different Y181 conformations while the third one are with Y181C modification[14]. Ligand based VS are also useful tools for development of HIV RT inhibitors although we are mainly discussing the structure based VS in this paper [15].

Based on the large number of HIV RT crystal structures, discovery of novel RT inhibitors through VS seems more reasonable than ever before. Also, the increasing number of compounds is very attractive to researchers who are engaged in VS. Besides discovery of lead compounds with RT inhibitory activity, more studies can be performed with VS. As mentioned in the above, inhibitors against RT mutant were selected using VS. VS can be applied to approach the issue of drug resistance. Drug resistance is a serious problem in AIDS treatment. It is very difficult for the drug development scientists to catch up with the step of mutations of drug resistance. With the assistance of VS, the issue of drug resistance may be better understood.

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